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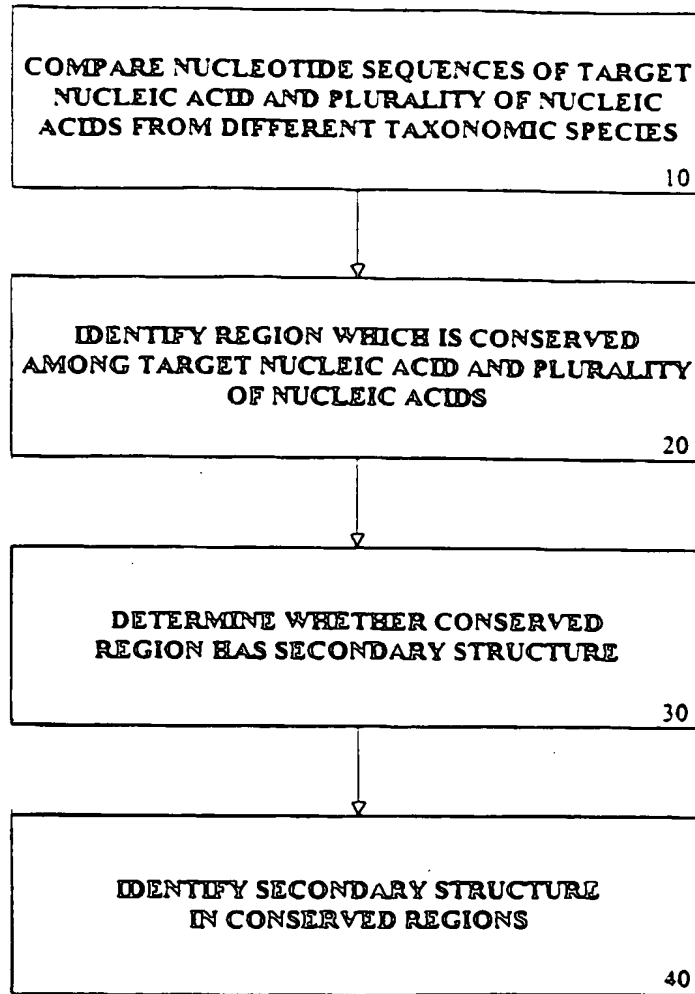


FIGURE 1

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Find Neighbors
and Assemble
Flow Diagram

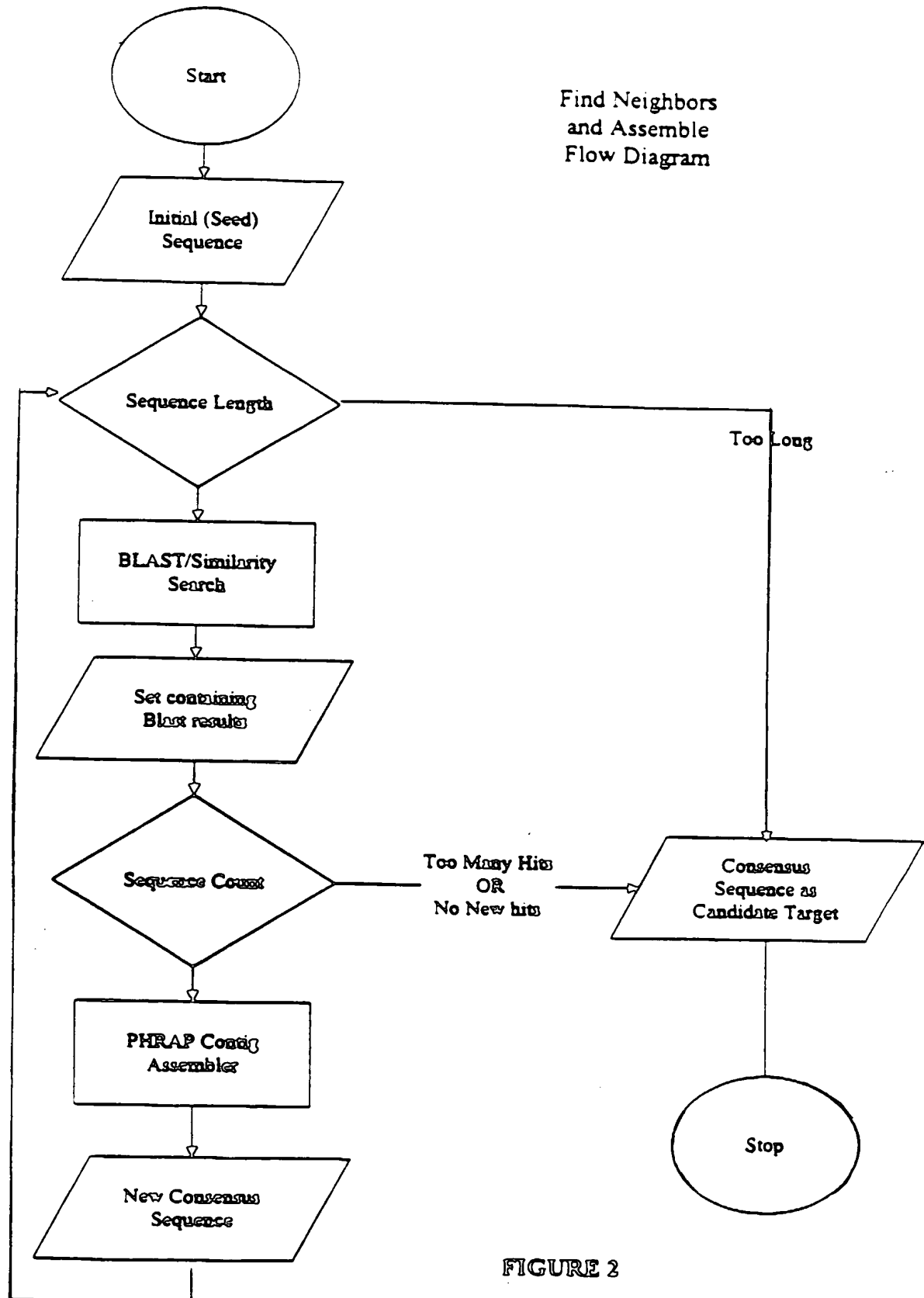


FIGURE 2

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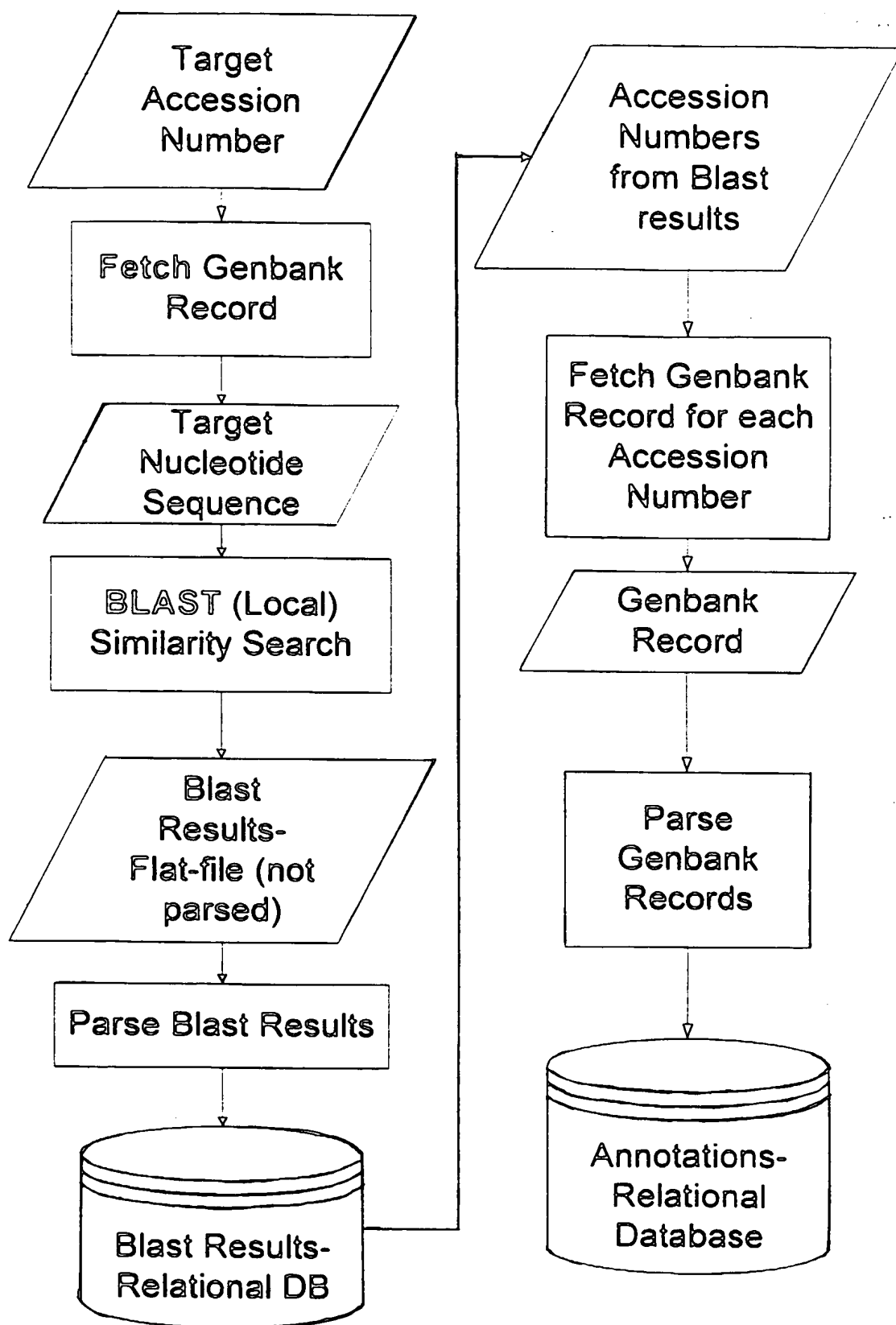


Figure 3

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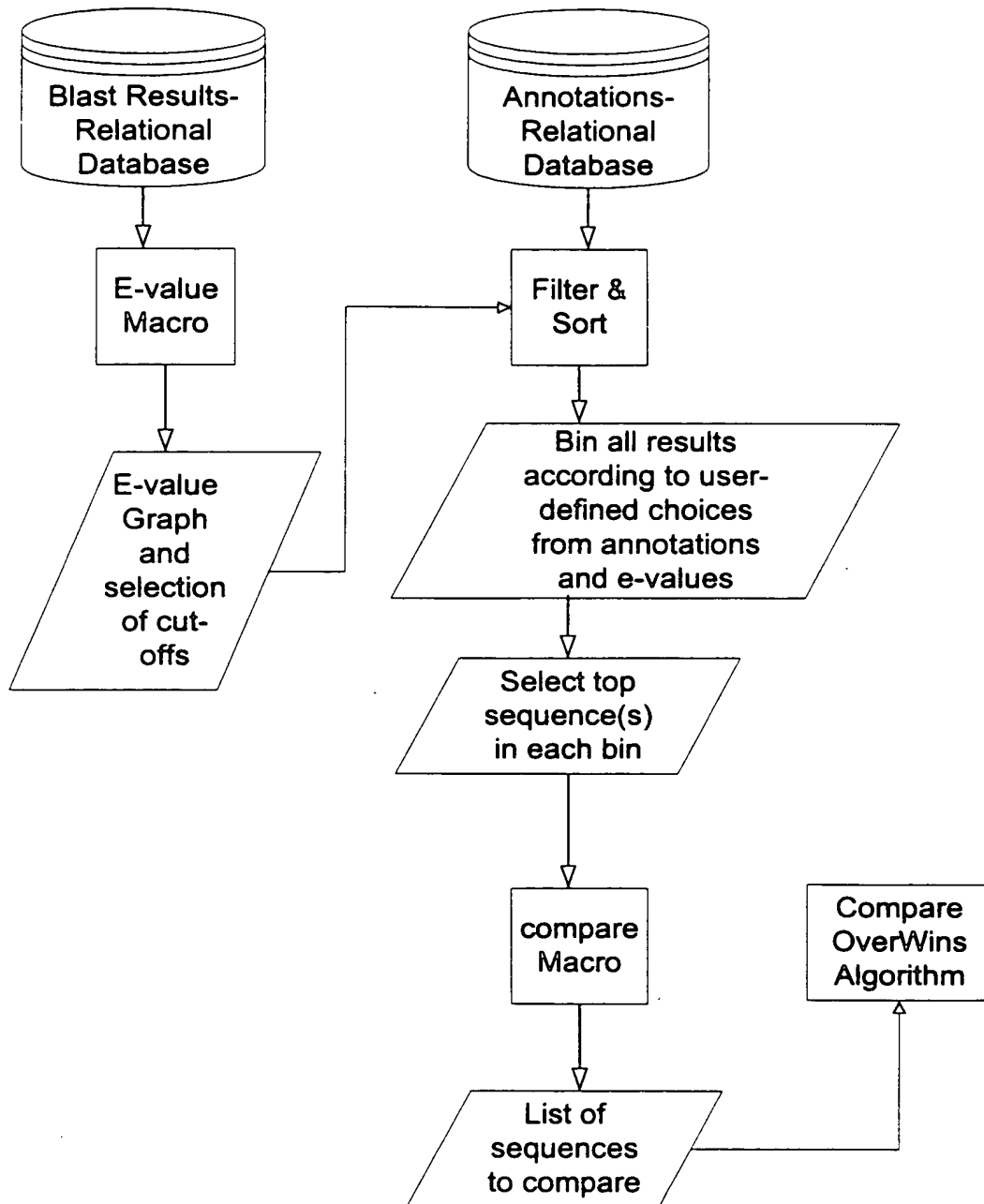
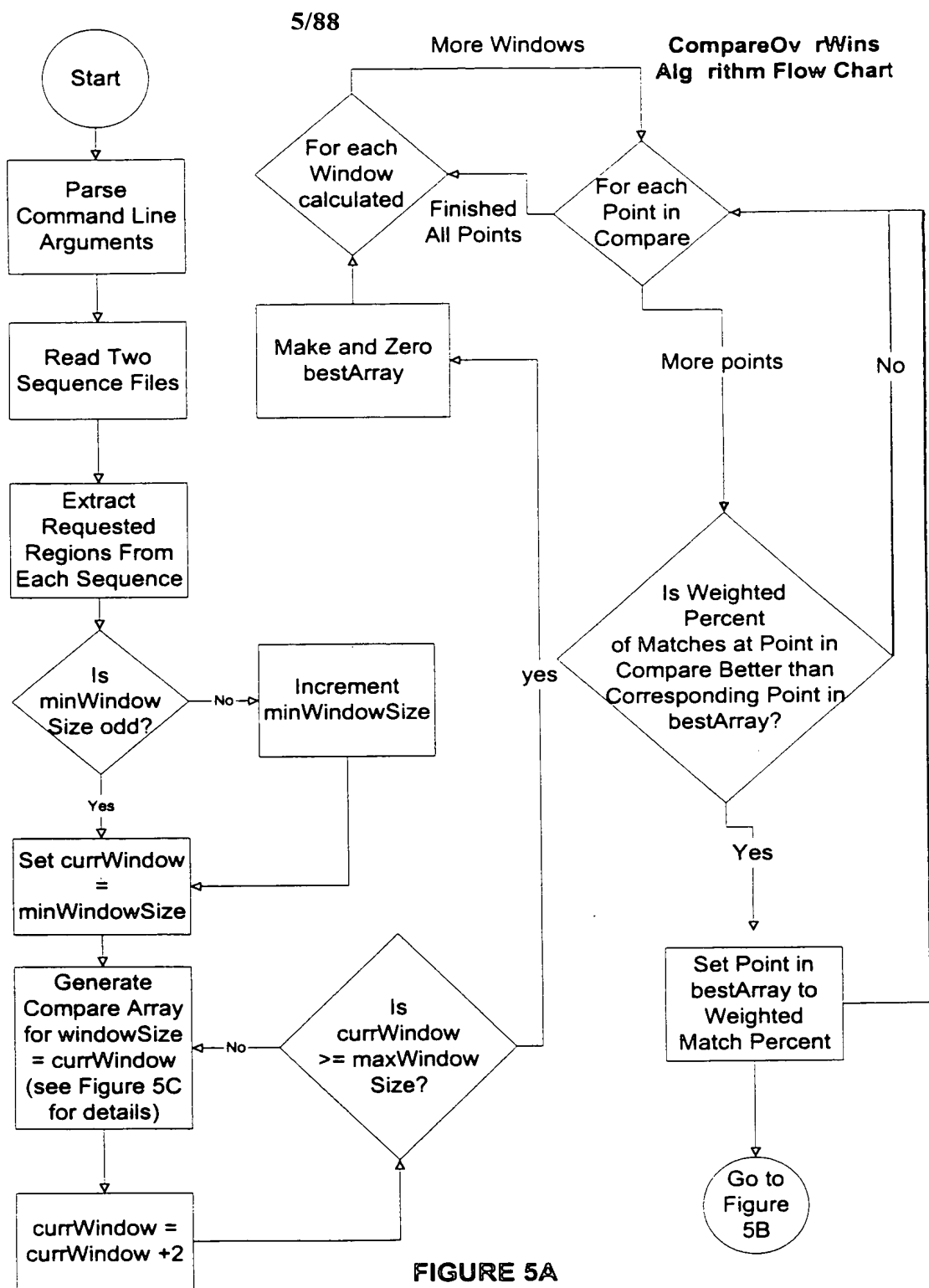


FIGURE 4



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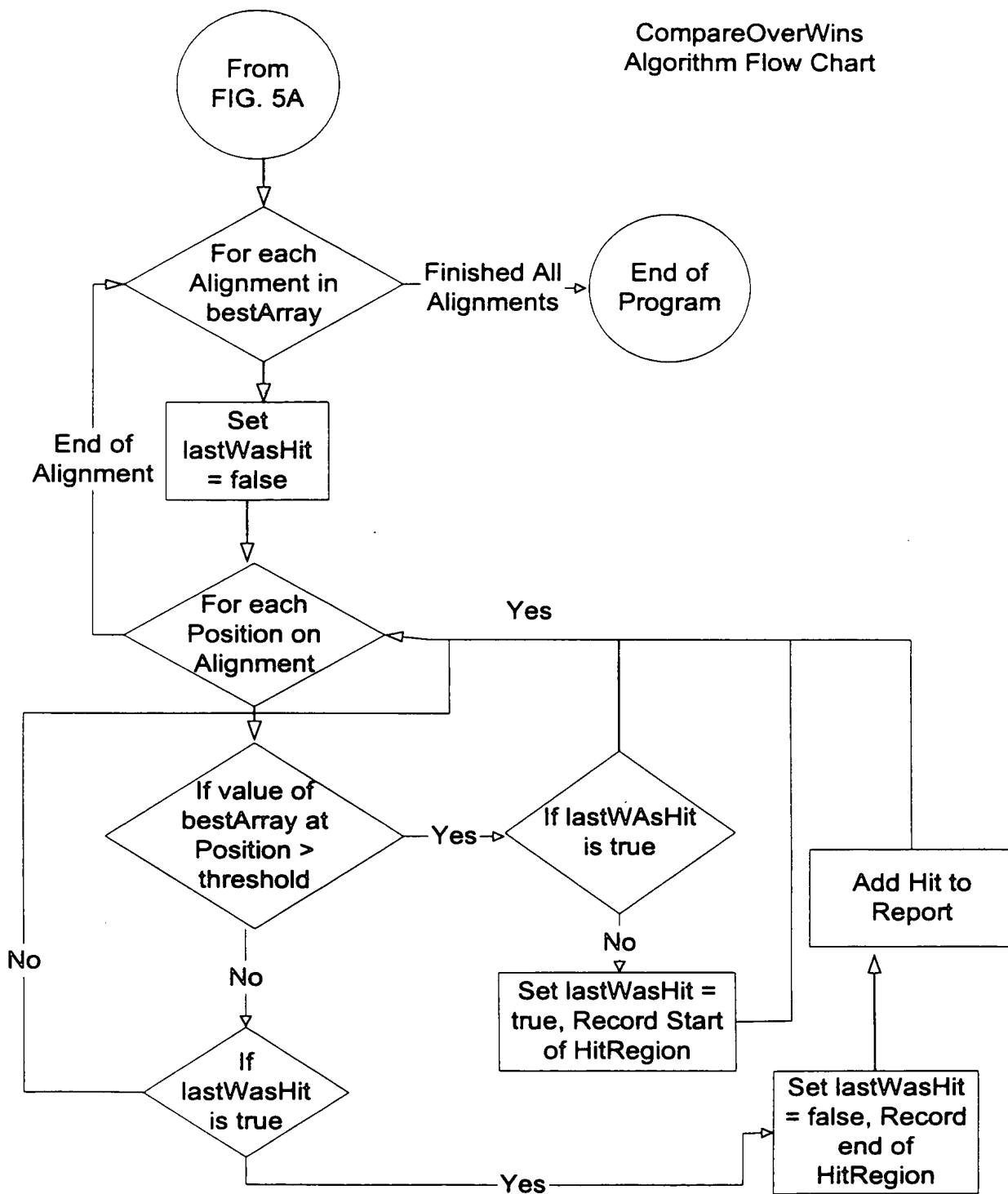


FIGURE 5B

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Compare Overlapping Windows Algorithm Flow Chart Basic Compare

Input:
 Sequence A length a
 Sequence B length b
 Window Size

Output:
 Array of size a by b of unsigned chars (0-255)
 Each point represents the number of matches in the
 window at that alignment and position

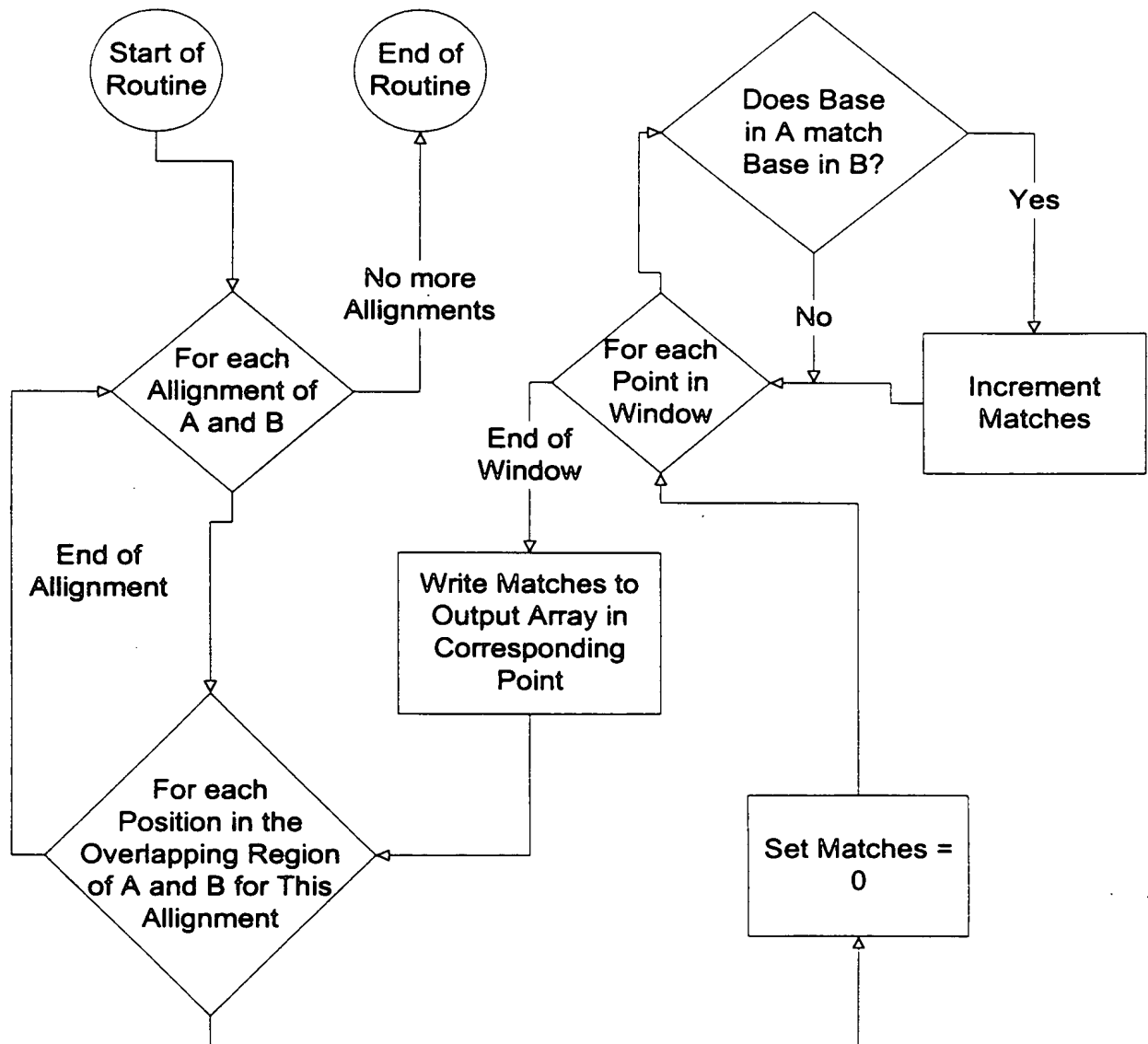


FIGURE 5C

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FIGURE 5D

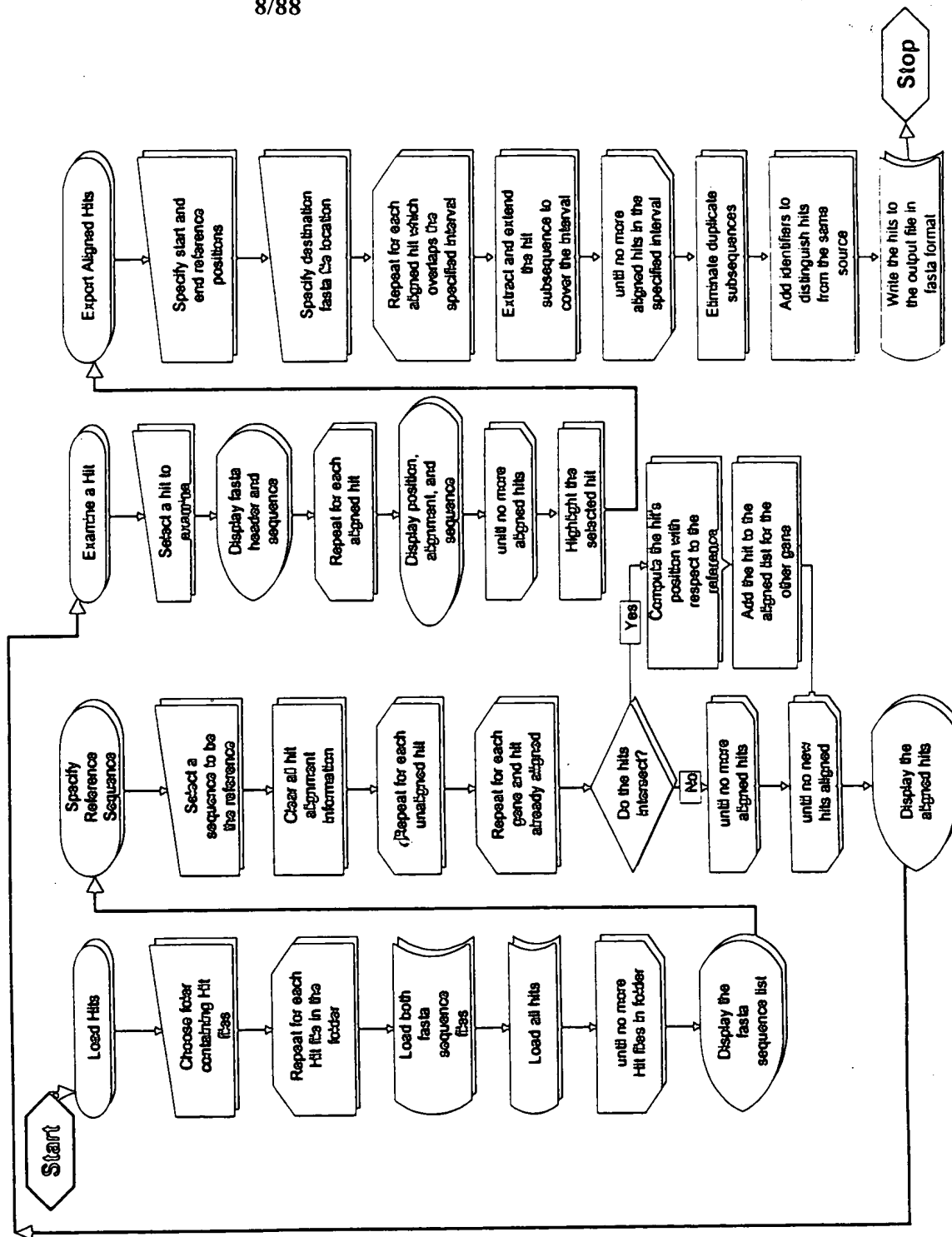
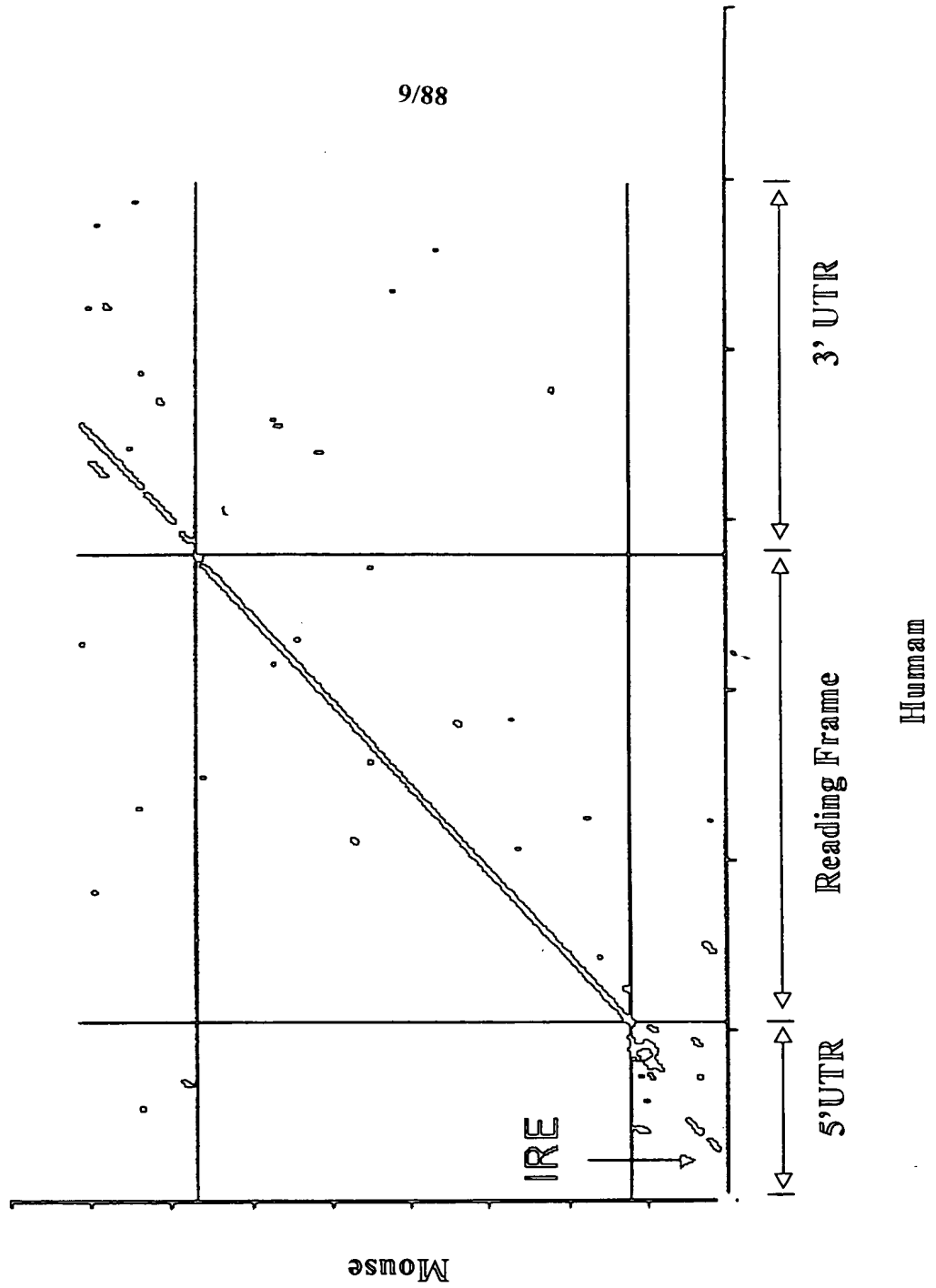


Figure 6



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Self Complementation Analysis - Single Sequence

3'	G	A	C	G	A	A	G	U	U	G	U	C	A	C	G	A	A	C	C	U	A	C	C	5'
23	*	&	*	*	&	*	*	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
22	&	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
21	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
20	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
19	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
18	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
17	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
16	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
15	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
14	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
13	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
12	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
11	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
10	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
9	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
8	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
7	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
6	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
5	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
4	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
3	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
2	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
1	*	&	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
5'	C	U	G	C	U	U	C	A	A	C	G	U	C	A	C	G	A	A	C	C	U	A	C	C

Figure 7

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Self Complementarity Comparisons

13 ortholog overlay

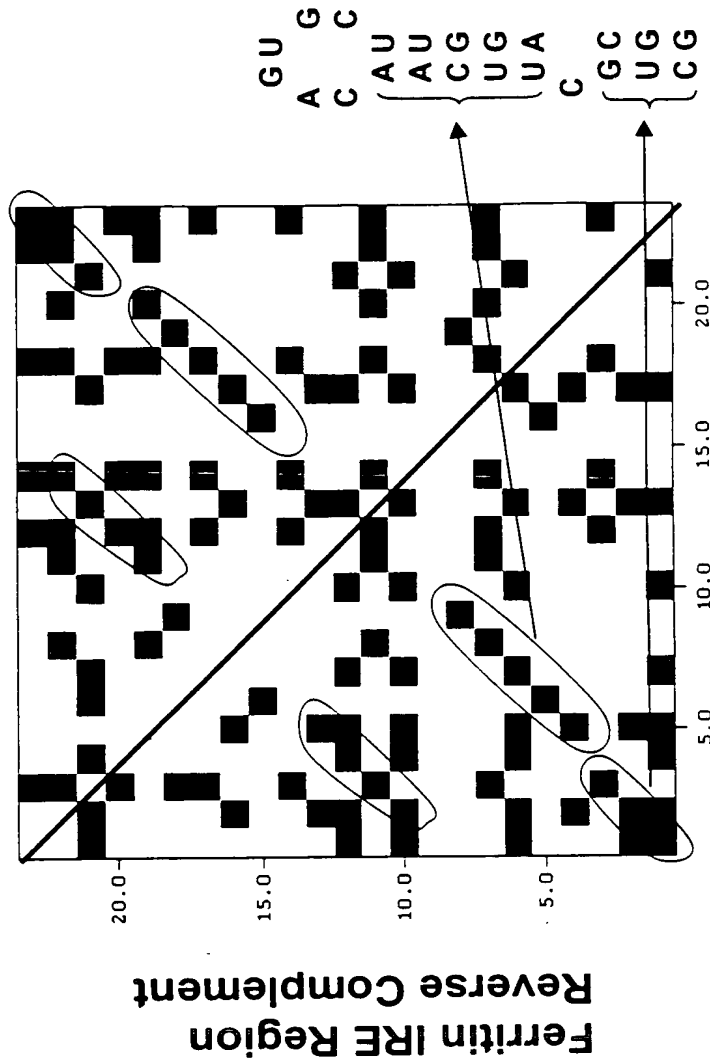


Figure 8

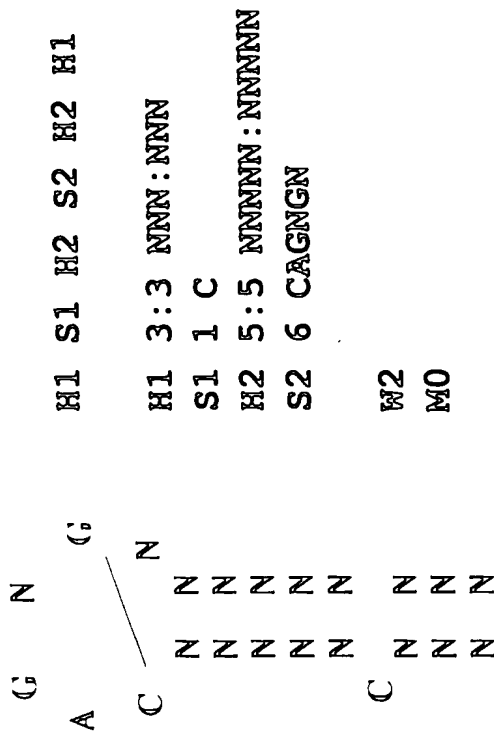
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Figure 9

IRE String descriptor

This descriptor allows for

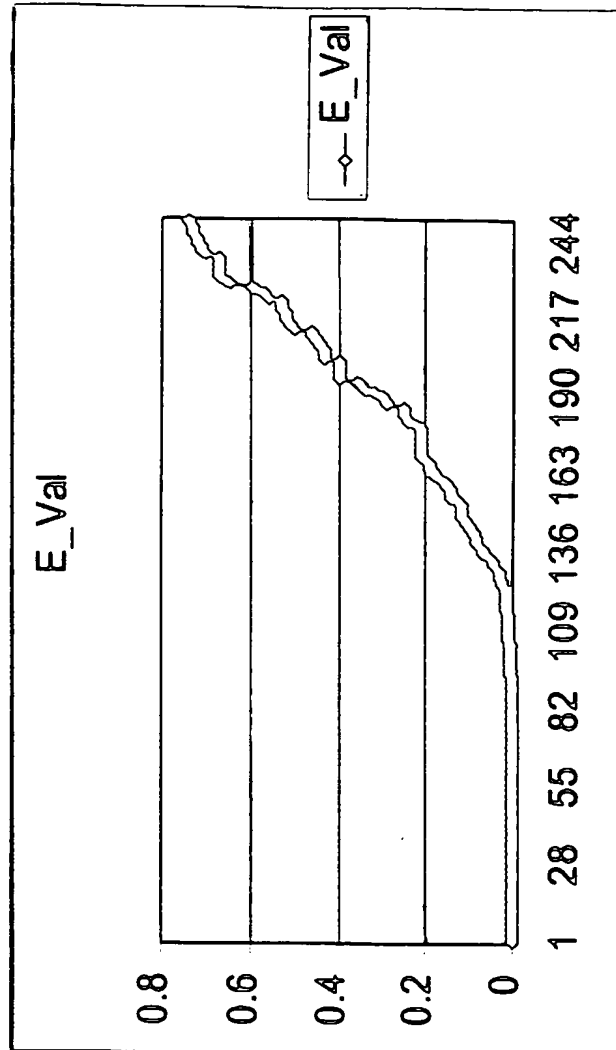
- a wobble (W) of 2
- no mismatches.
- N can be any nucleotide
- H refers to the stem region
- S refers to the single stranded region.



IRE
 Stem-loop Model

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Figure 10



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Figure 11

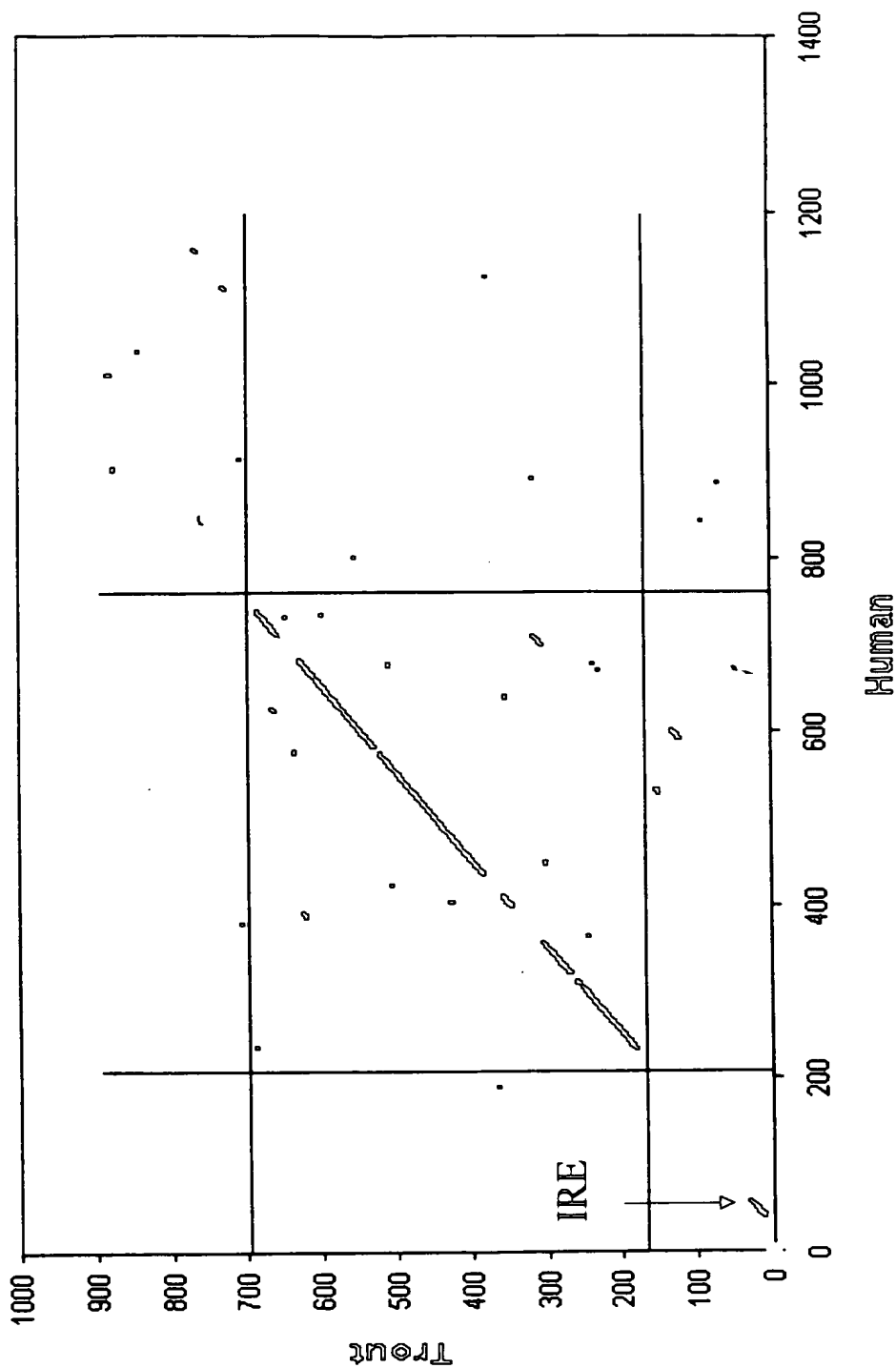
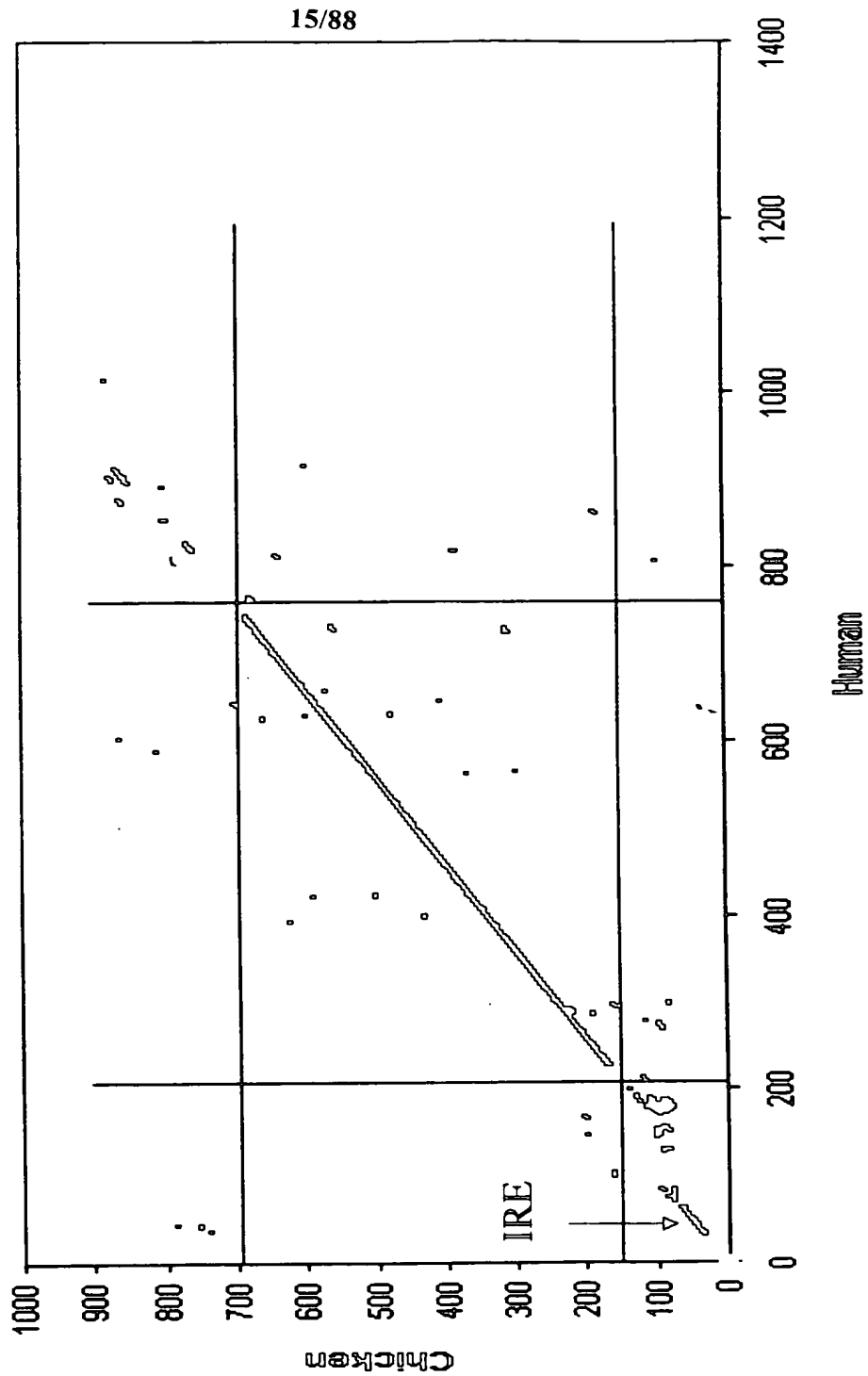


Figure 12



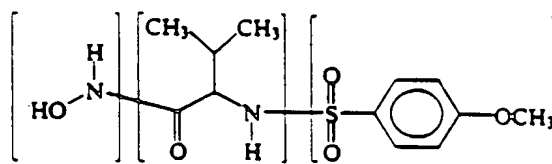
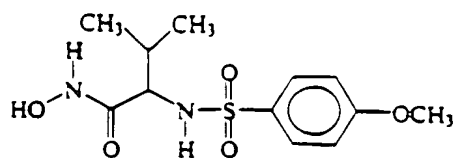
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	HUMAN PIC	HUMAN MOUSE RAT	CHICKEN	TROUT SALMON	XENOPUS FROG	FLY	MOSQUITO
	G-U A G C C	G-U A G C C	G-U A G C C	G-U A G C A	G-U A G C U	G-U A G C U	G-U A G C U
	A-U A-U C-G U-G U-A C	A-U A-U C-G U-A U-A C	A-U A-U C-G U-G G-A C	A-U A-U C-G U-A U-A C	A-U A-U C-G U-A U-A C	C-G G-U C-G G-U U-A C	C-G G-U U-A G-U U-A C
	G-C U-G C-G	G-C U-G C-G	G-C U-G C-G	G-C U-G U-G	G-C U-G U-G	U-A U-A C-G	U-A U-A C-G
HUMAN PIC	No	No	Yes	Yes	Yes	No	No
HUMAN MOUSE RAT	No	No	Yes	Yes	Yes	No	No
CHICKEN			No	Yes	Yes	No	No
TROUT SALMON				No	Yes	Yes	Yes
XENOPUS FROG					No	Yes	Yes
FLY						No	Yes
MOSQUITO							No

Figure 13

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Compound CI



	F _i	F _{ii}	F _{iii}
Molecular formula	H ₂ NO	C ₅ H ₉ NO	C ₇ H ₇ O ₃ S

Figure 14

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Addition of fragments to yield compounds

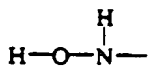
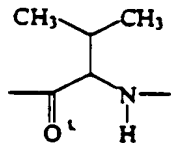
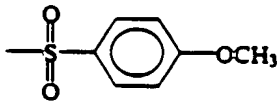
Fragment Identifier	Table			
	Structure	Name	Molecular formula	Other
F _i		Hydroxylamine	H ₂ NO	...
F _{ii}		Amino acid	C ₃ H ₉ NO	...
F _{iii}		Sulfonyl	C ₇ H ₇ O ₃ S	...

Figure 15

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Reagents	Identifier	Name	Properties
$\text{H}-\text{O}-\text{NH}_2$ or $\textcircled{\text{P}}-\text{O}-\text{NH}_2$	Ri	Hydroxylamine	...
$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ \text{CH} \\ \\ \text{HO}-\text{C}(=\text{O})-\text{CH}-\text{N}-\text{FMOC} \\ \\ \text{H} \end{array}$	Rii	FMOC blocked amino acid	...
$\begin{array}{c} \text{O} \\ \\ \text{Cl}-\text{S}-\text{C}_6\text{H}_4-\text{OCH}_3 \end{array}$	Riii	Sulfonylchloride	...

$\textcircled{\text{P}}$ = Solid support

Figure 16

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Transformation

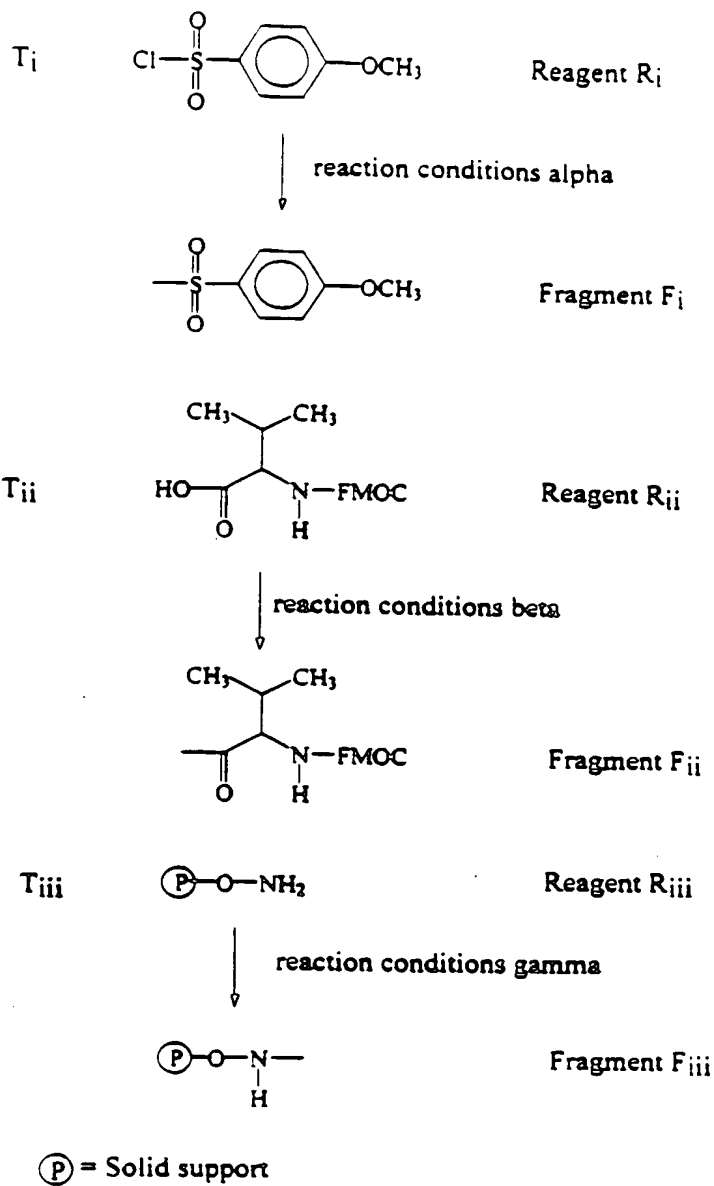


Figure 17

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Common Fragment / Different Reagents and Transformations

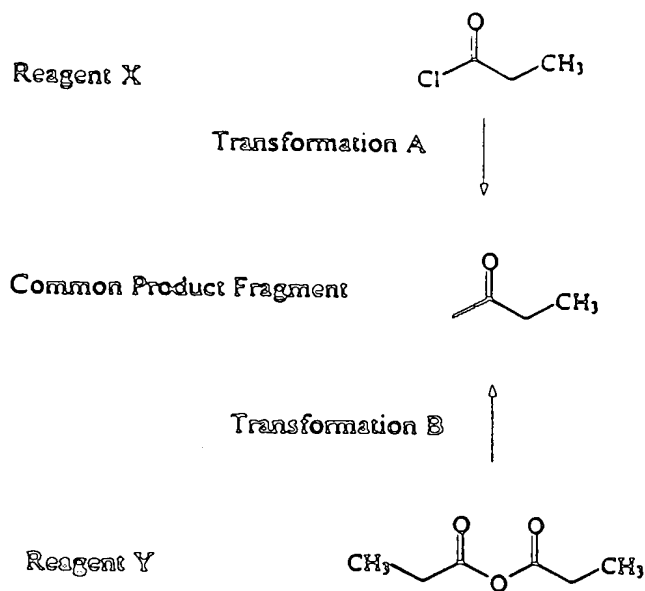


Figure 18

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Common Fragment / Different Reagents and Transformations

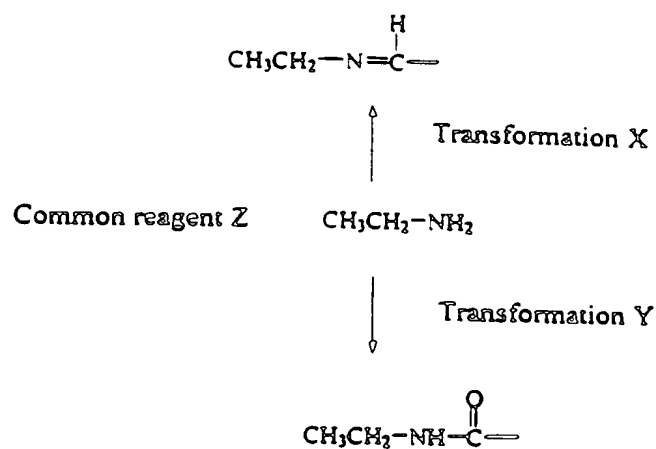


Figure 19A

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Common Reagent

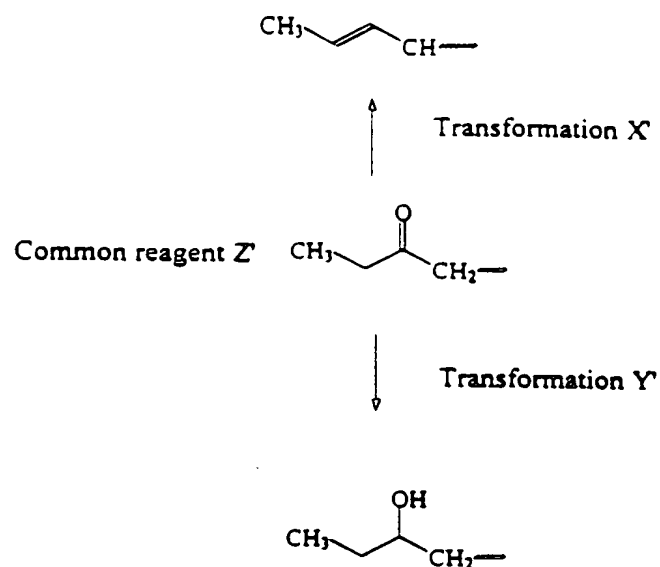


Figure 19B

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Symbolic addition of fragments to yield compound

<u>Symbolic Structure</u>	<u>Symbolic Identifier</u>	<u>Molecular formula</u>
---------------------------	----------------------------	--------------------------

Fragment



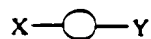
F_i'

$C_uH_vN_w \dots$



F_{ii}'

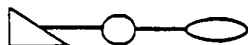
$C_uH_vN_w \dots$



F_{iii}'

$C_uH_vN_w \dots$

Compound



CI'

$C_uH_vN_w \dots$

$$\begin{aligned}
 &\text{Molecular formula } F_i' \\
 &+ \\
 &\text{Molecular formula } F_{ii}' \\
 &+ \\
 &\text{Molecular formula } F_{iii}' \\
 &= \text{Molecular formula } CI'
 \end{aligned}$$

Figure 20

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Symbolic Reagent Table


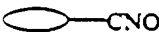


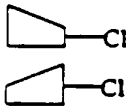
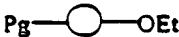


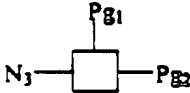
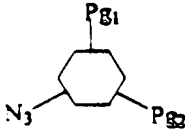
<u>Identifier</u>	<u>Name</u>	<u>Structure</u>	<u>Molecular formula</u>
R1	xxx	 Cl	xxx
R2	...		...
R3	...	 Cl	...
R4	...	 Br	...
R5	...	 Cl Cl	...
R6	...	 Pg—OEt	...
R7	...	 Pg—Cl	...
R8	...	 Pg—Br	...
R9	...	 Pg1 N3—Pg2	...
R10	...	 Pg1 N3—Pg2	...

Figure 21

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Symbolic Fragment Table




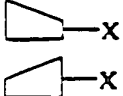
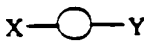

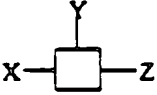
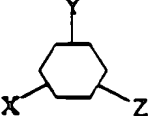
Identifier	Symbolic Structure	Molecular formula	Molecular Weight
F1		xxx	xxx
F2	
F3	
F4	
F5	
F6	
F7	
F8	

Figure 22

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Symbolic Transformation Table



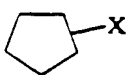

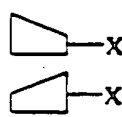
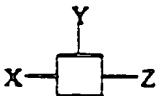
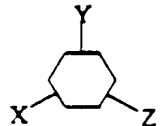
Identifier		Symbolic Reactions	Reagent
T1	F1	 $\xrightarrow{\text{R1}}$	conditions α
T2	F2	 $\xrightarrow{\text{R2}}$	conditions β
T3	F3	 $\xrightarrow{\text{R3}}$	conditions α
T4	F3	 $\xrightarrow{\text{R4}}$	conditions α
T5	F4	 $\xrightarrow{\text{R5}}$	conditions α
T6	F5	$\text{X} - \text{O} - \text{Y}$ $\xrightarrow{\text{R6}}$	conditions ϵ
T7	F5	$\text{X} - \text{O} - \text{Y}$ $\xrightarrow{\text{R7}}$	conditions α
T8	F6	$\text{X} - \text{C} - \text{Y}$ $\xrightarrow{\text{R8}}$	conditions α
T9	F7	 $\xrightarrow{\text{R9}}$	conditions γ
T10	F8	 $\xrightarrow{\text{R10}}$	conditions γ

Figure 23

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Single Compounds and Mixtures

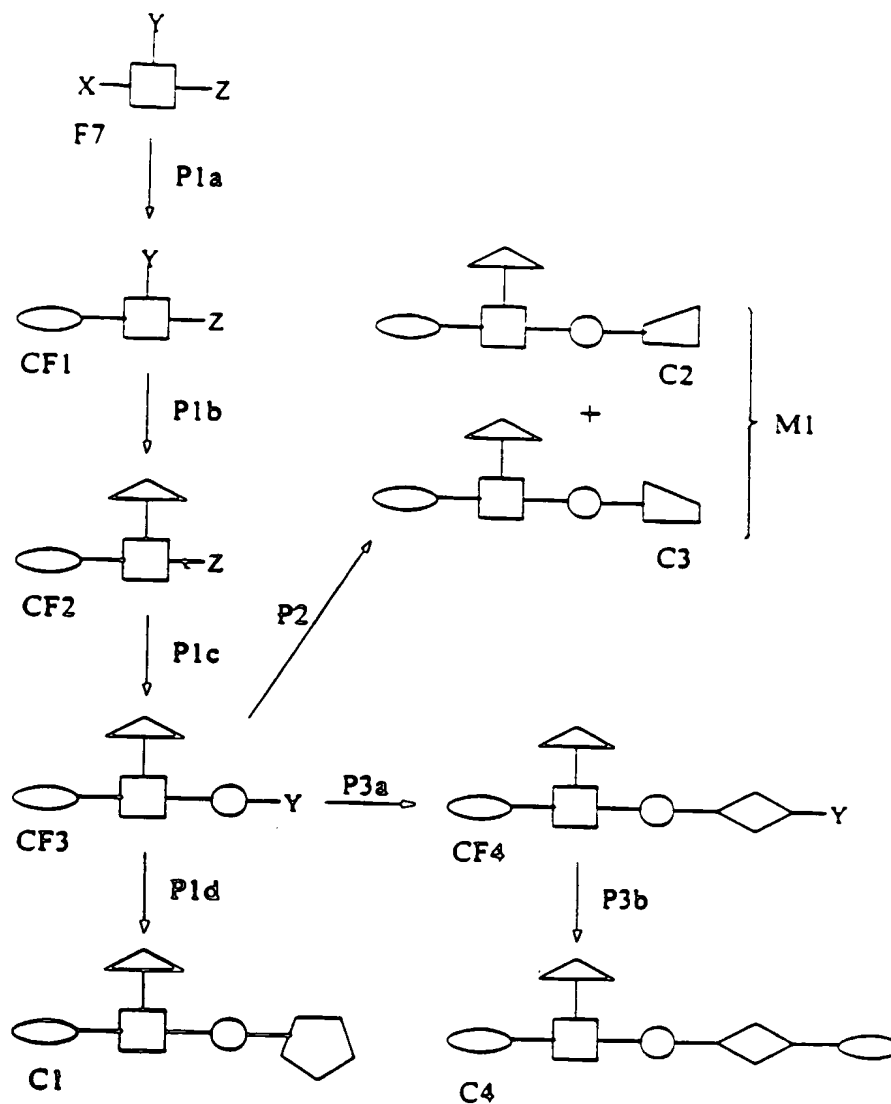


Figure 24

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Mixture 2

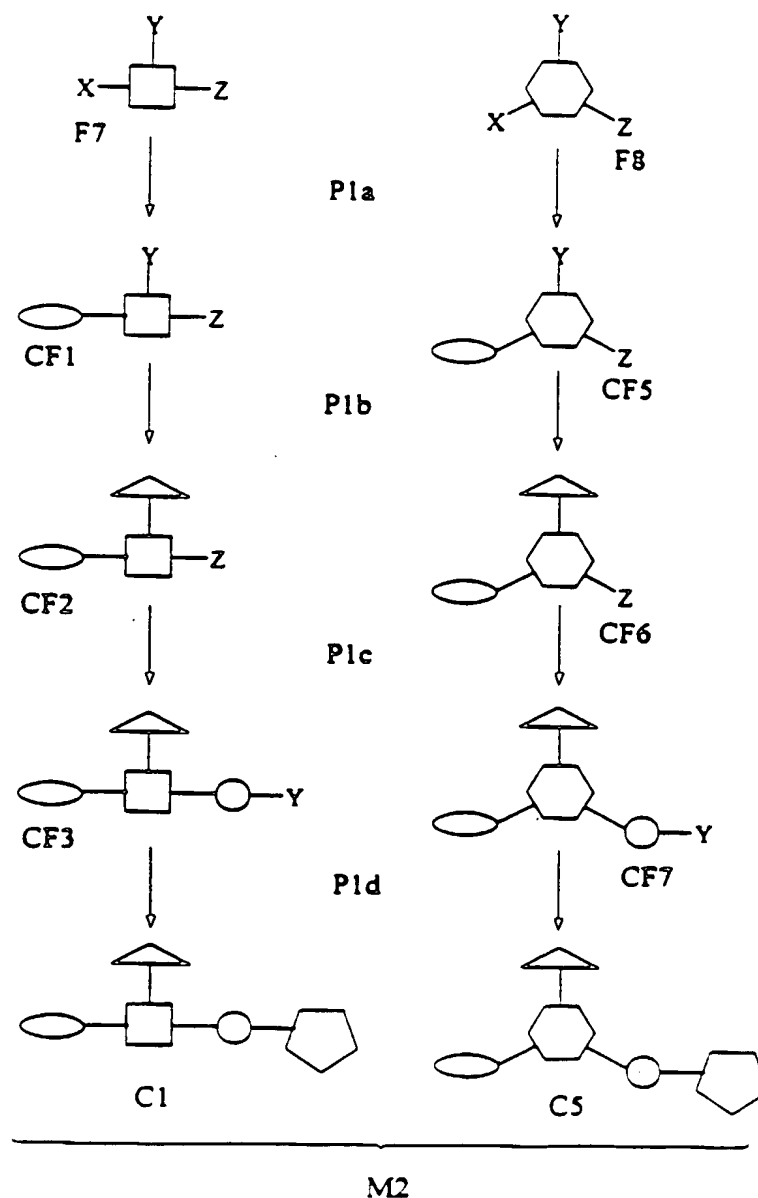


Figure 25

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Mixture 3

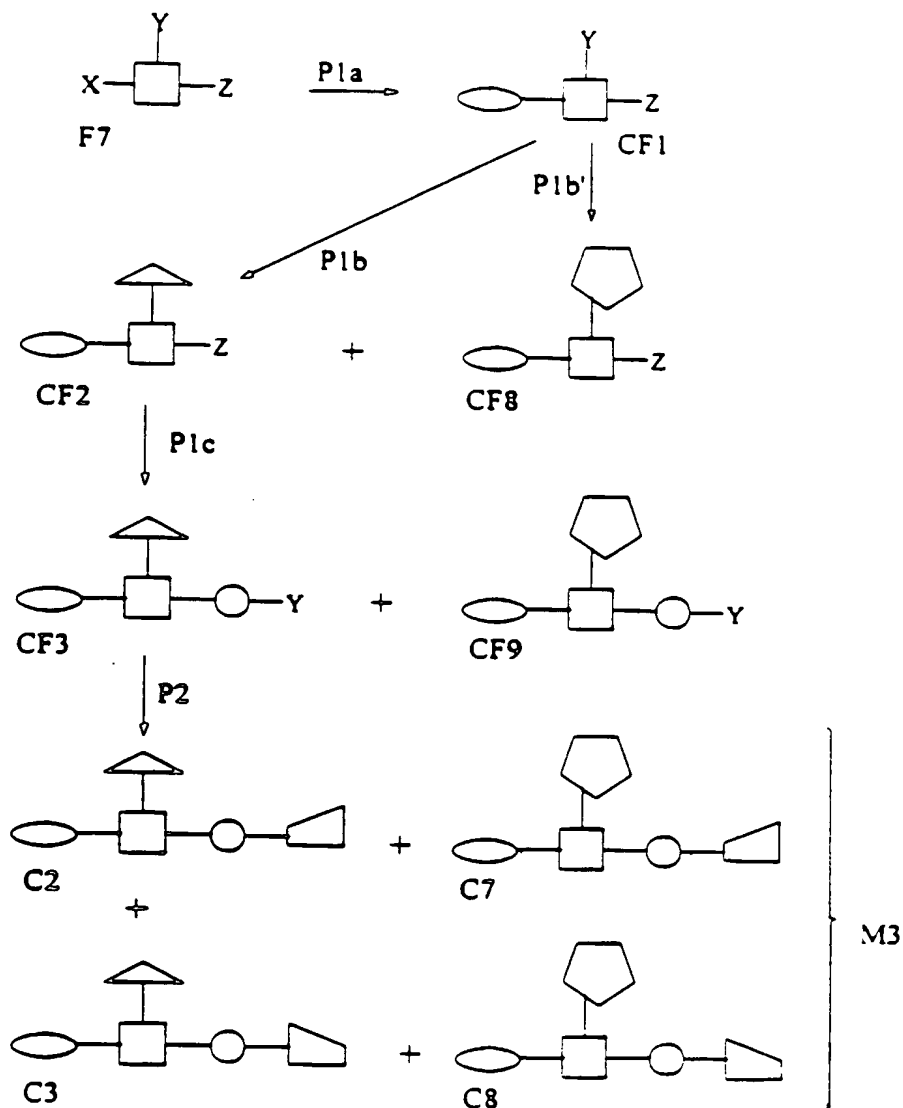
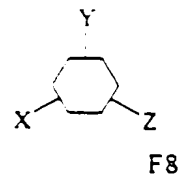
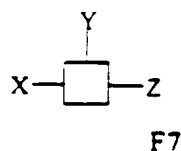


Figure 26

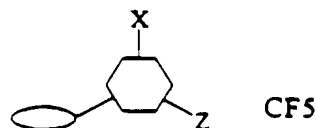
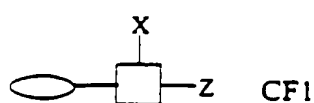
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Mixture 4

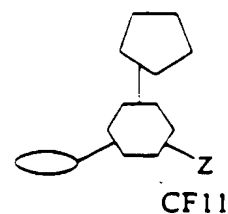
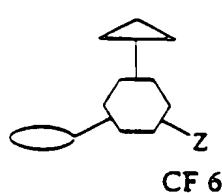
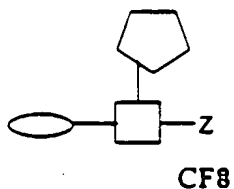
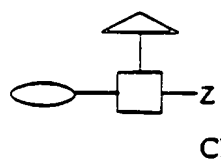
2 Starting Fragments



2 Complex Fragments



4 Complex Fragments



8 Complex Fragments

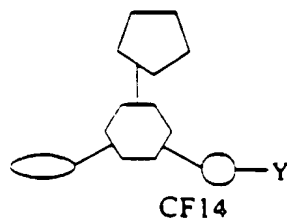
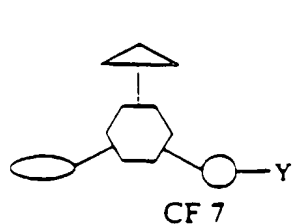
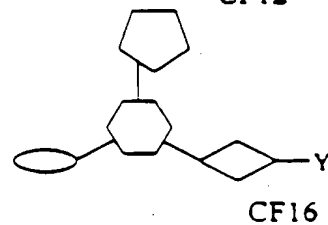
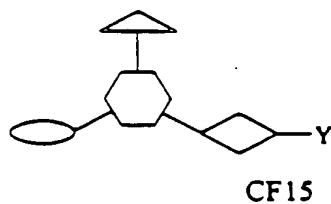
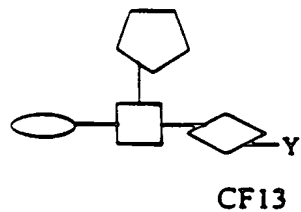
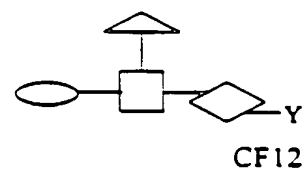
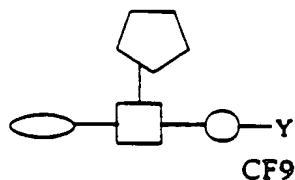
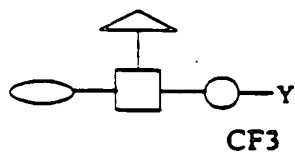


Figure 27A

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Mixture 4 (continued)

16 compounds

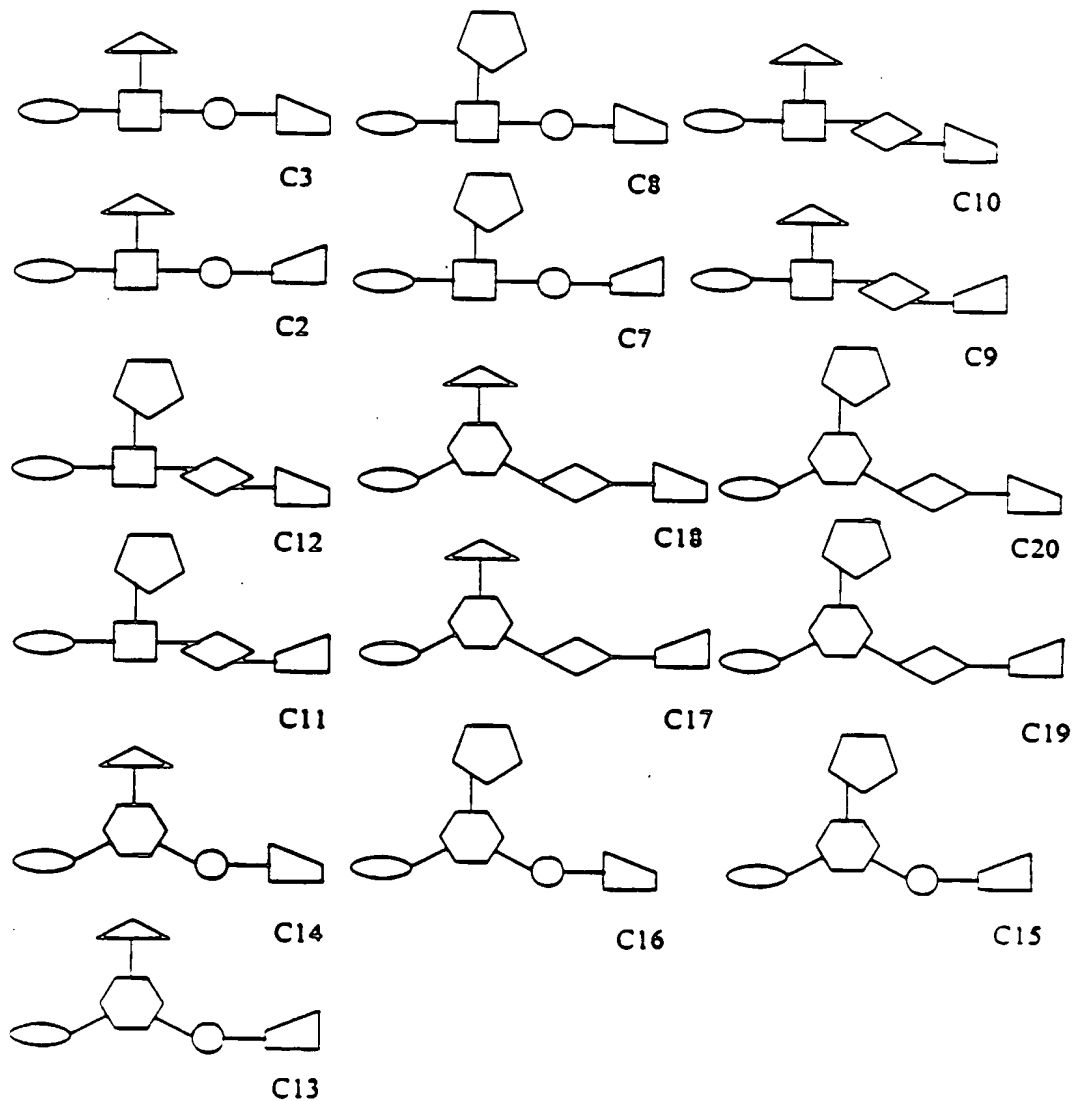


Figure 27B

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Tracking Table for Compound C1

(a) By Fragments:

n	n+1	n+2
F7	F2 F1 F5	F3

(b) By Transformations:

Synthesis Path 1

n	n+1	n+2
T9	T2 T1 T6	T3

Synthesis Path 2

n	n+1	n+2
T9	T2 T1 T7	T3

Synthesis Path 3

n	n+1	n+2
T9	T2 T1 T6	T4

Synthesis Path 4

n	n+1	n+2
T9	T2 T1 T7	T4

Figure 28

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Tracking Table

Tracking M1

Step 1

T9		
----	--	--

Step 2

T9	T2	
----	----	--

Step 3

T9	T2 T1	
----	----------	--

Step 4

T9	T2 T1 T7	
----	----------------	--

Step 5

T9	T2 T1 T7	T5 ¹
----	----------------	-----------------

C2

Step 5

T9	T2 T1 T7	T5 ²
----	----------------	-----------------

C3

Figure 29

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Tracking Table

Tracking M2

Step 1

n	n+1	n+2
T9		

Step 1

n	n+1	n+2
T10		

Step 2

n	n+1	n+2
T9	T2	

Step 2

n	n+1	n+2
T10	T2	

Step 3

n	n+1	n+2
T9	T2 T1	

Step 3

n	n+1	n+2
T10	T2 T1	

Step 4

n	n+1	n+2
T9	T2 T1 T7	

Step 4

n	n+1	n+2
T10	T2 T1 T7	

Step 5

n	n+1	n+2
T9	T2 T1 T7	T4

Step 5

n	n+1	n+2
T10	T2 T1 T7	T4

C1

C5

Figure 30

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Tracking Table

Tracking M3

Step 1

T9		
----	--	--

Step 2

T9	T2	
----	----	--

Step 3

T9	T2 T1	
----	----------	--

Step 3

T9	T2 T3	
----	----------	--

Step 4

T9	T2 T1 T7	
----	----------------	--

Step 4

T9	T2 T3 T7	
----	----------------	--

Step 5

T9	T2 T1 T7	T5 ¹
C2		

Step 5

T9	T2 T1 T7	T5 ²
C3		

Step 5

T9	T2 T3 T7	T5 ¹
C7		

Step 5

T9	T2 T3 T7	T5 ²
C8		

Figure 31

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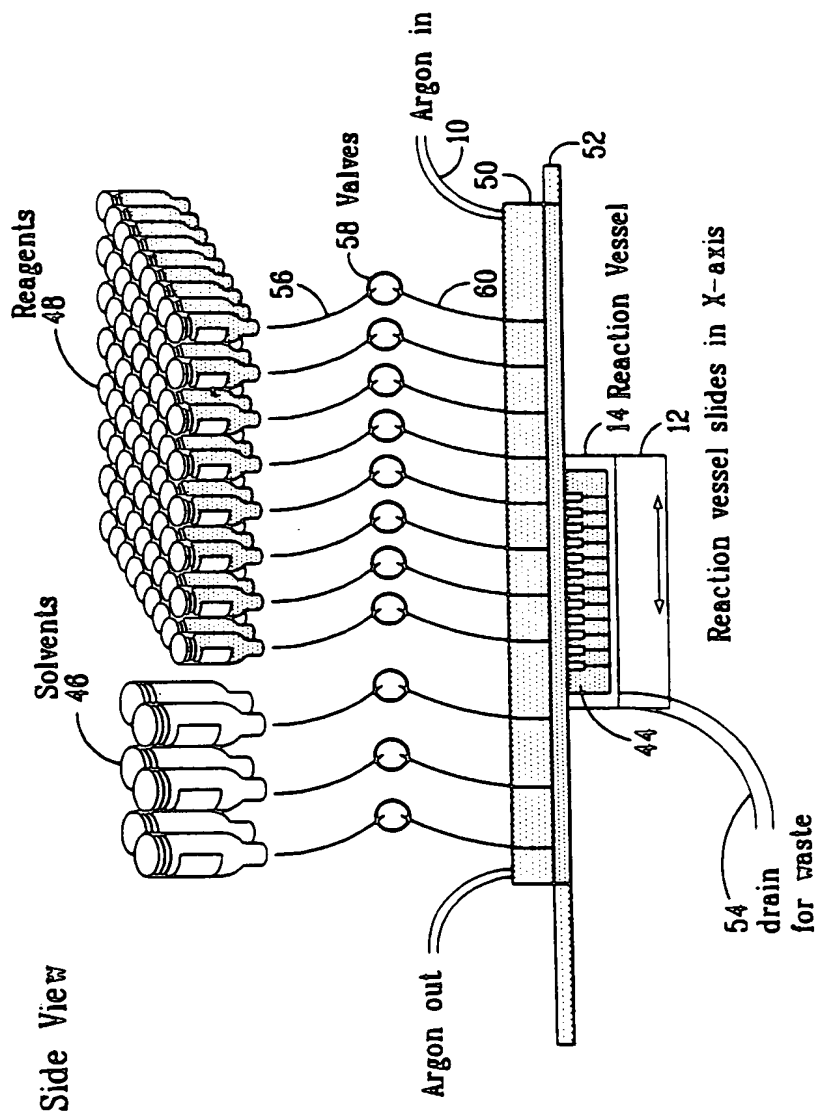


Figure 32

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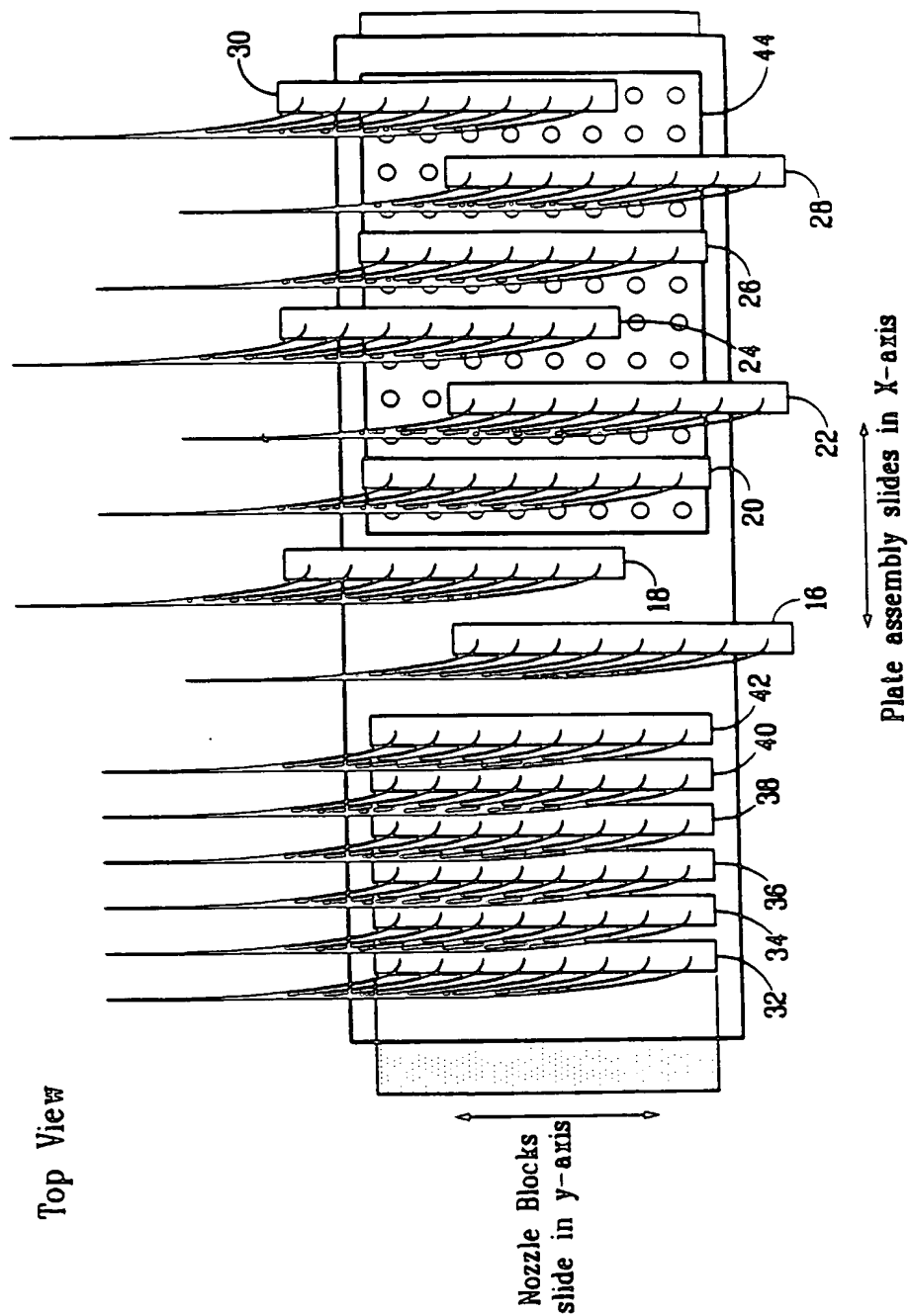


Figure 33

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Synthesis of hydroxamic acids from alcohol resin

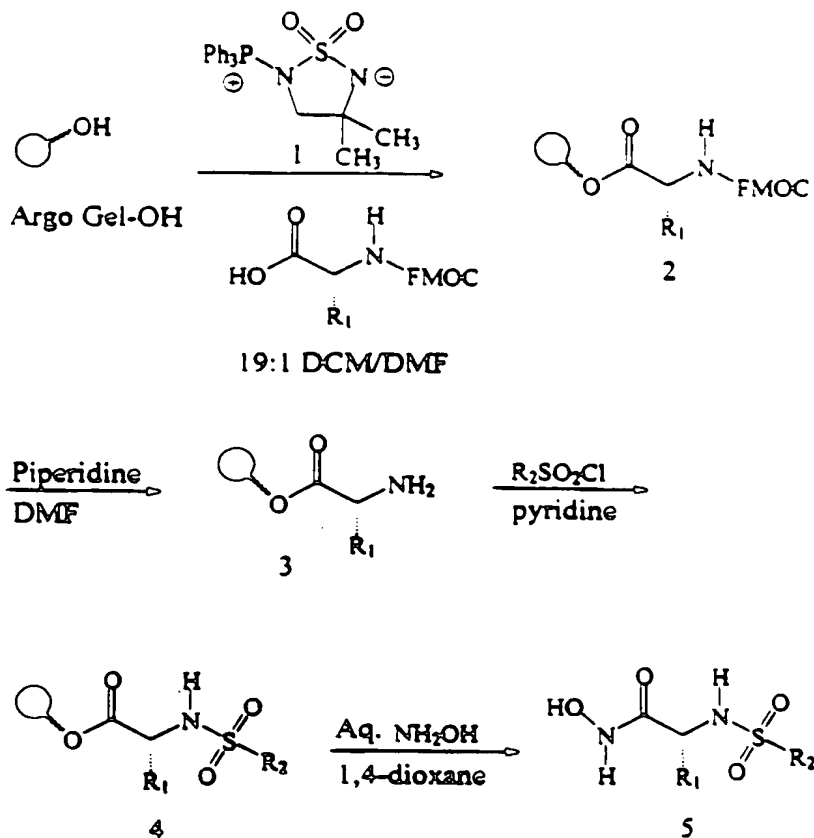


Figure 34

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Synthesis of hydroxamic acids from hydroxylamine resin

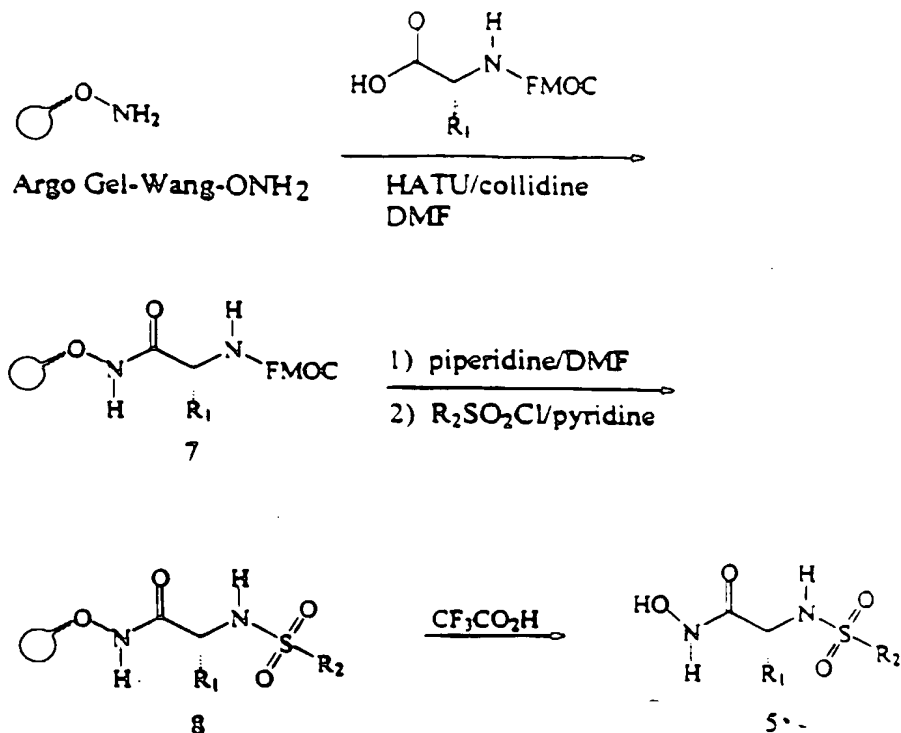


Figure 35

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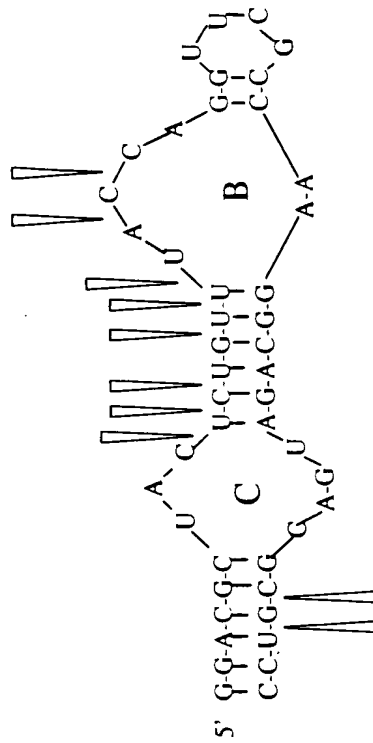


Figure 36

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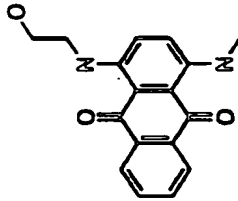
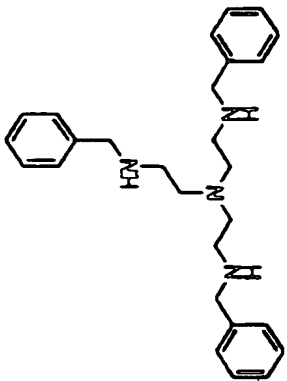
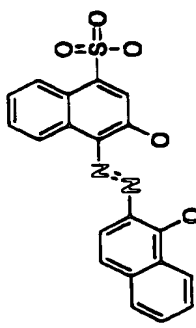
ACD Code	Structure	Calc. ΔG of binding (kcal/mole)	IC ₅₀ (μM)
00001199		-5.1	< 2
00192509		-8.5	< 2
00003934		-5.1	< 50

Figure 37

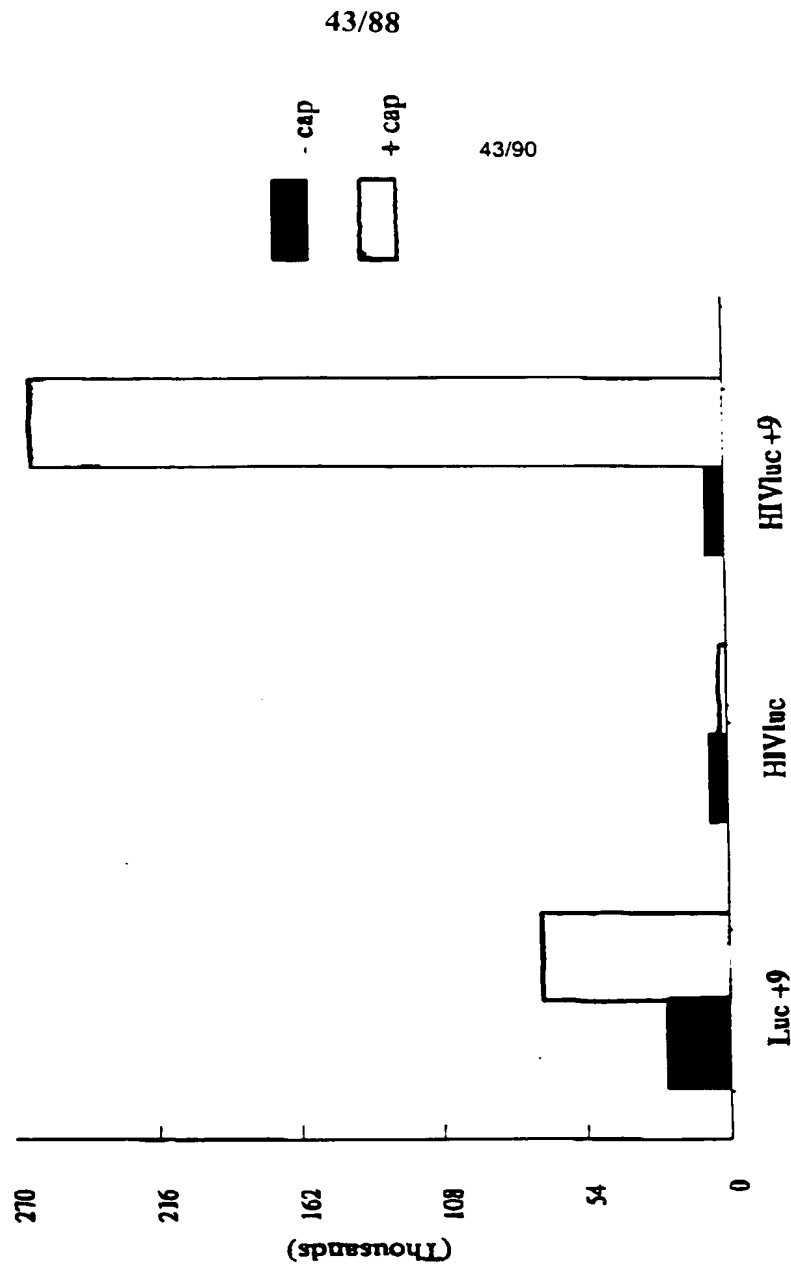


Figure 38A

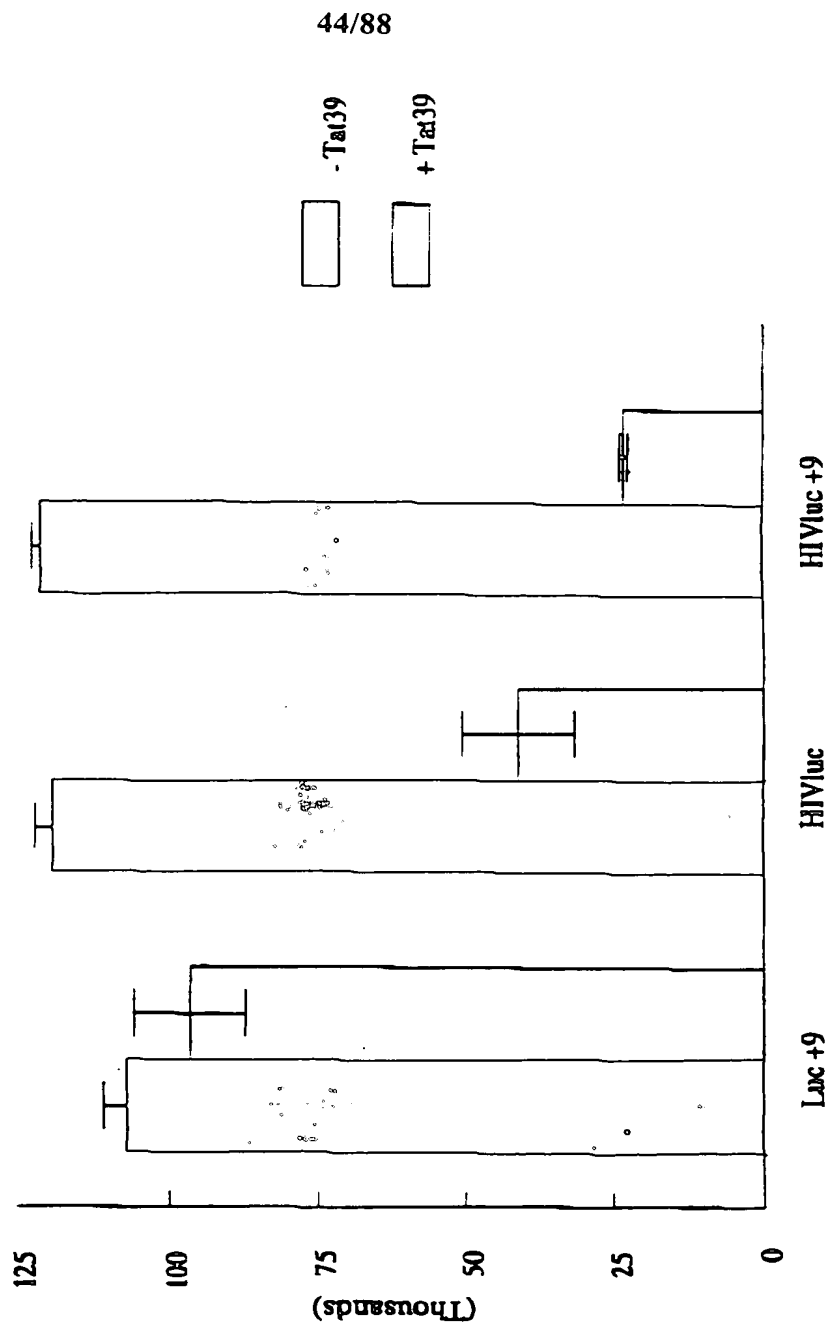


Figure 38B

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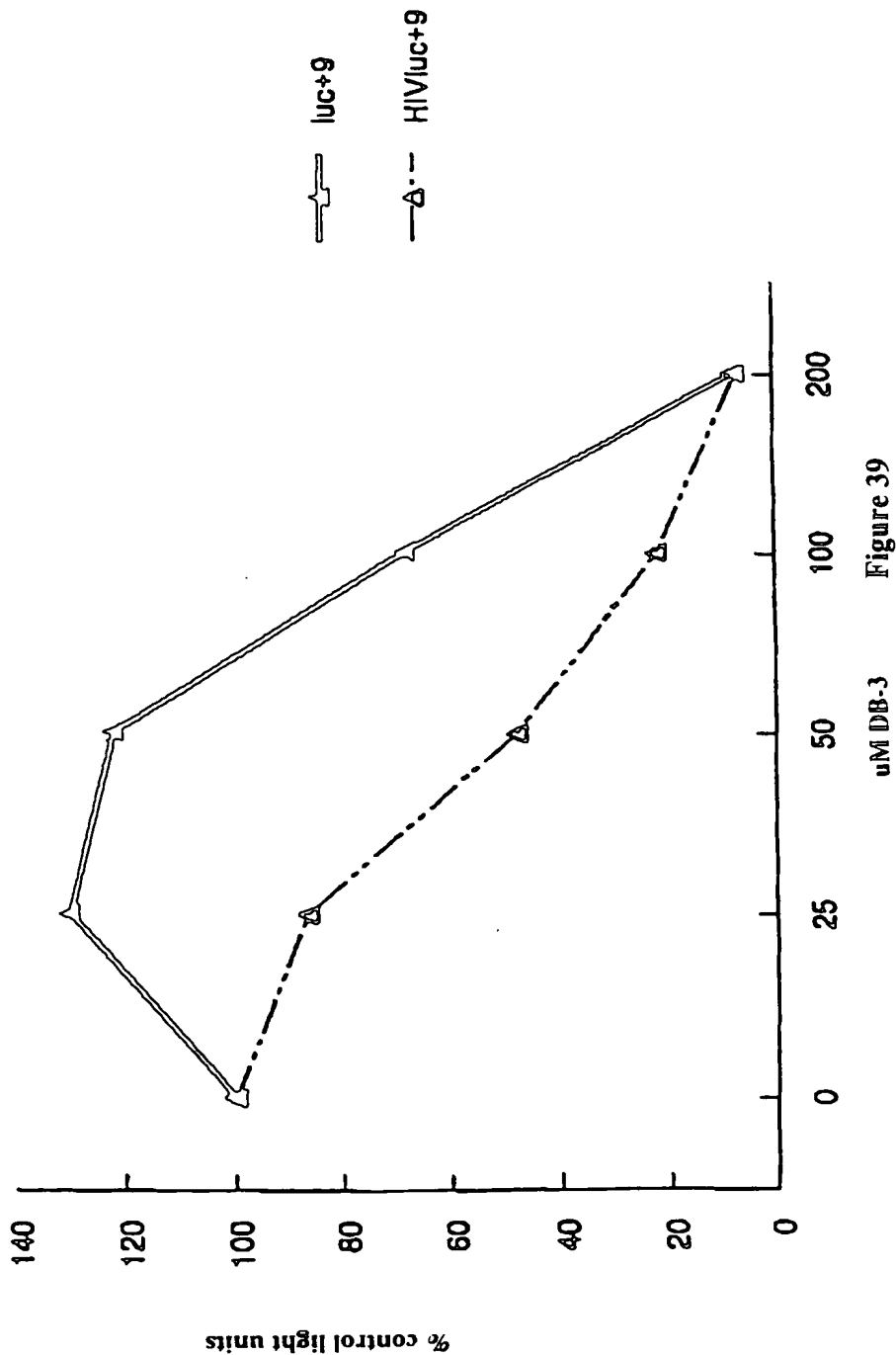


Figure 39

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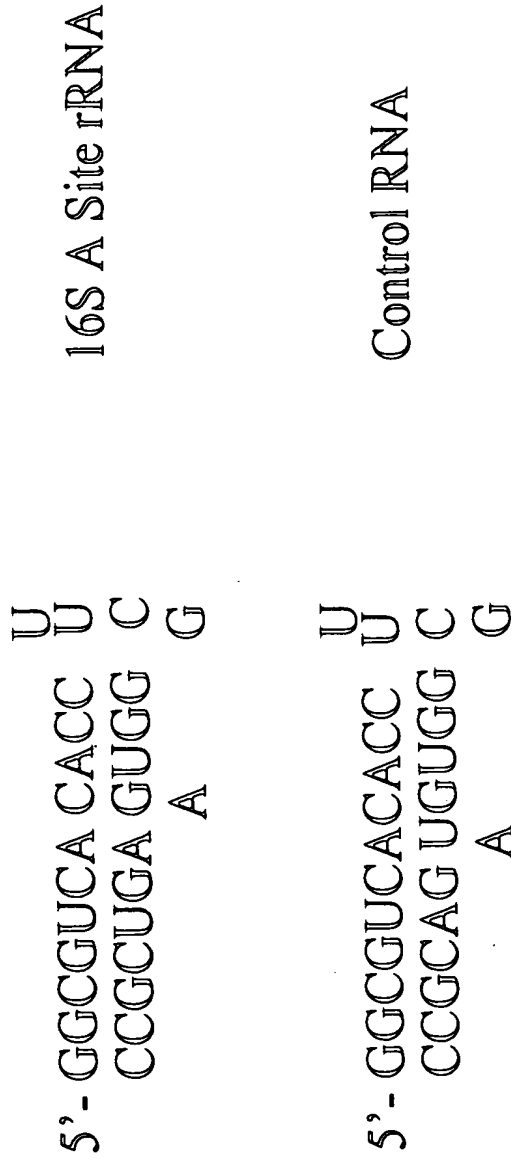


Figure 40

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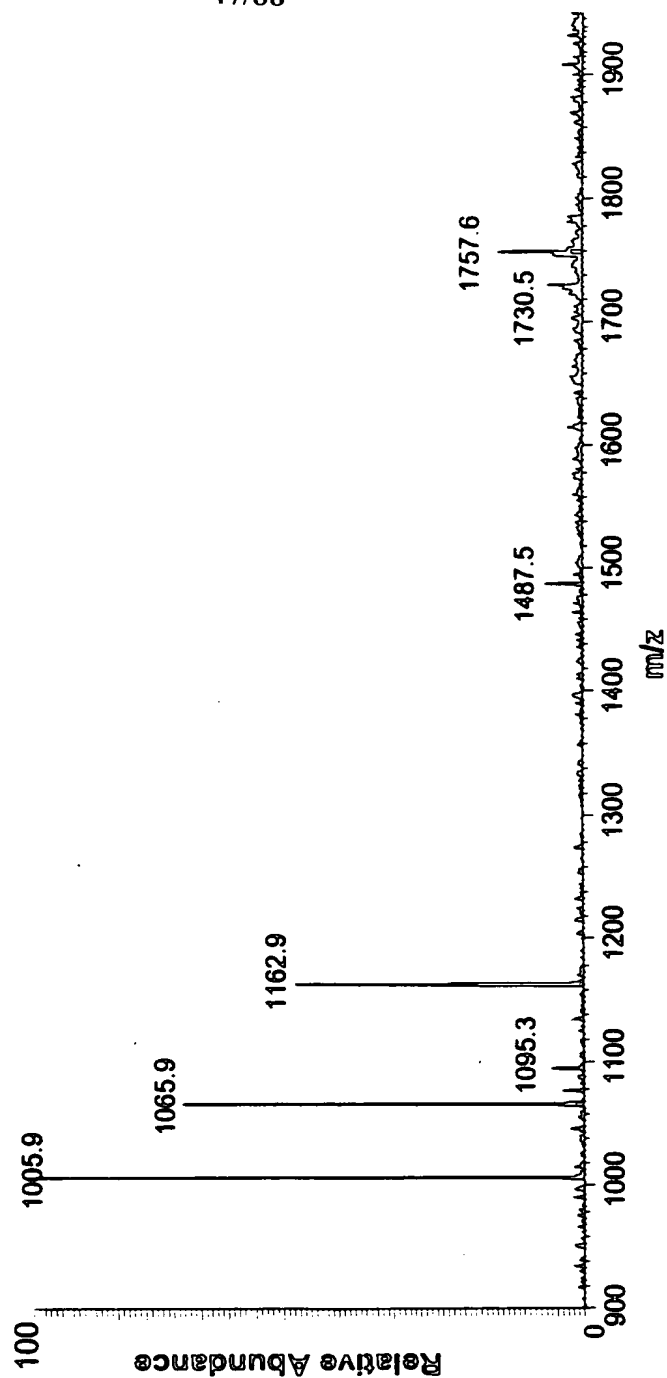


Figure 41A

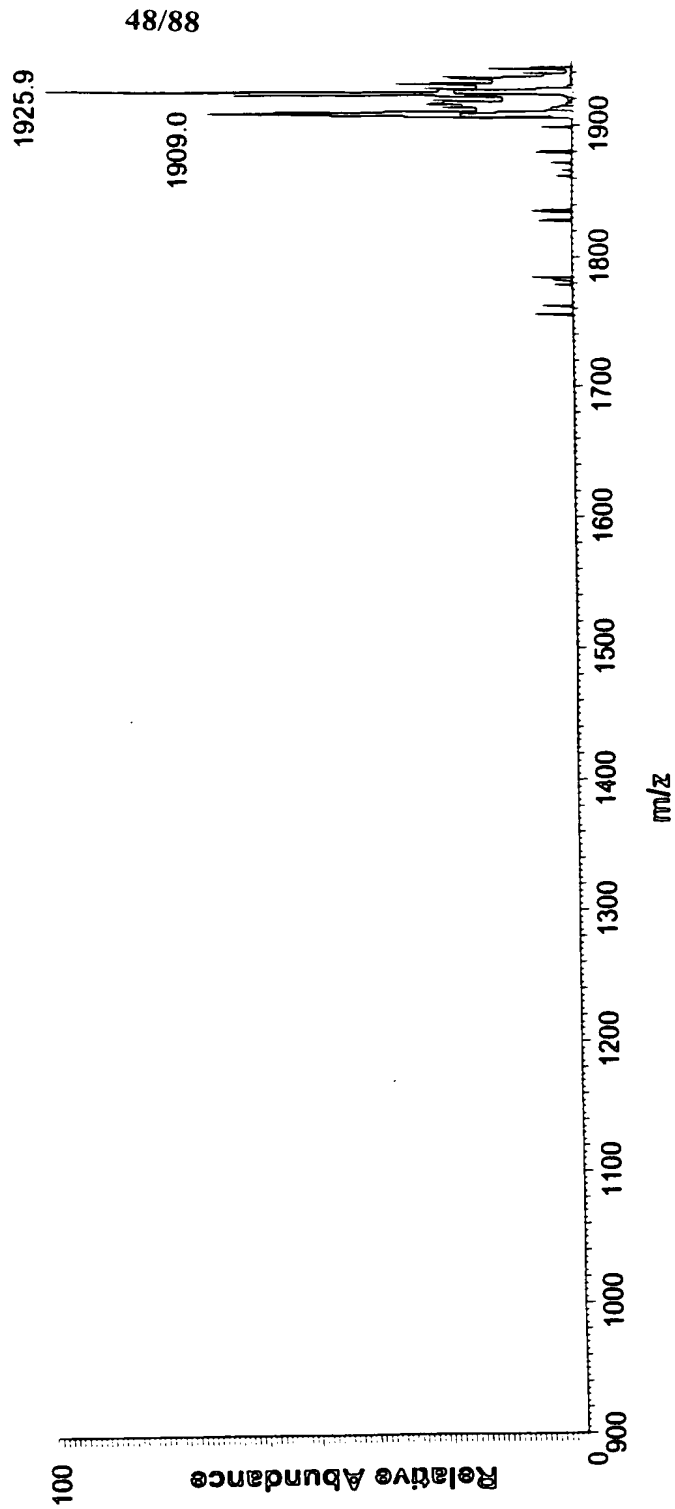


Figure 41B

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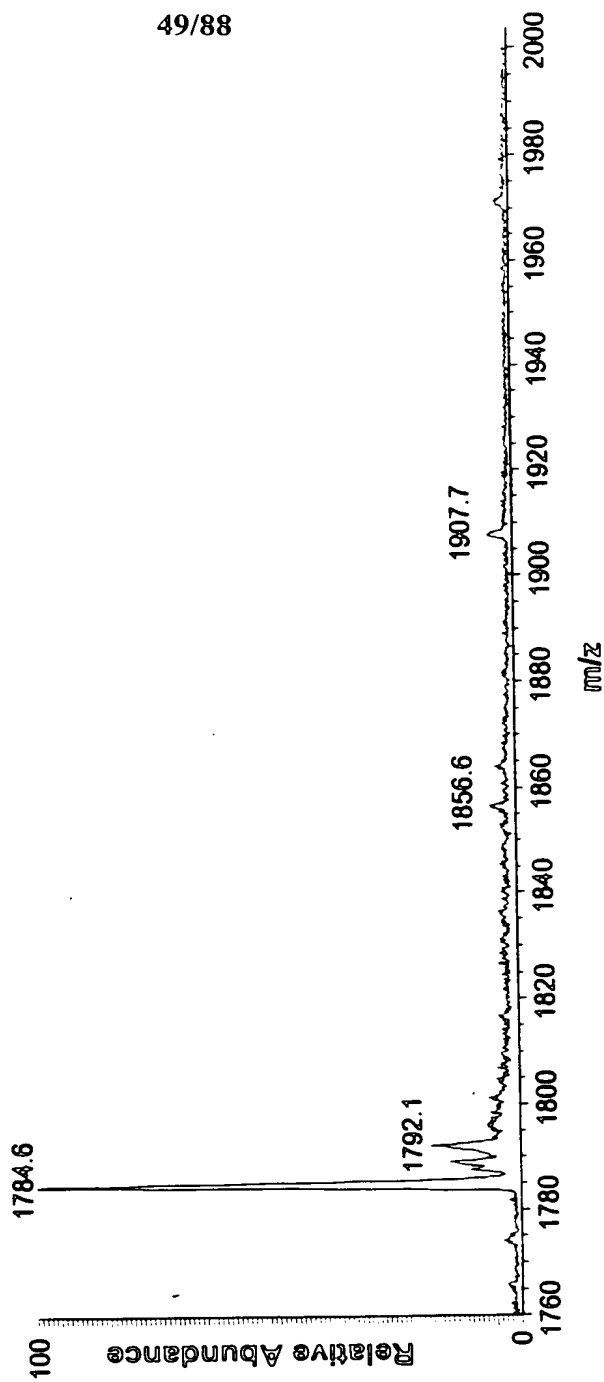


Figure 42A

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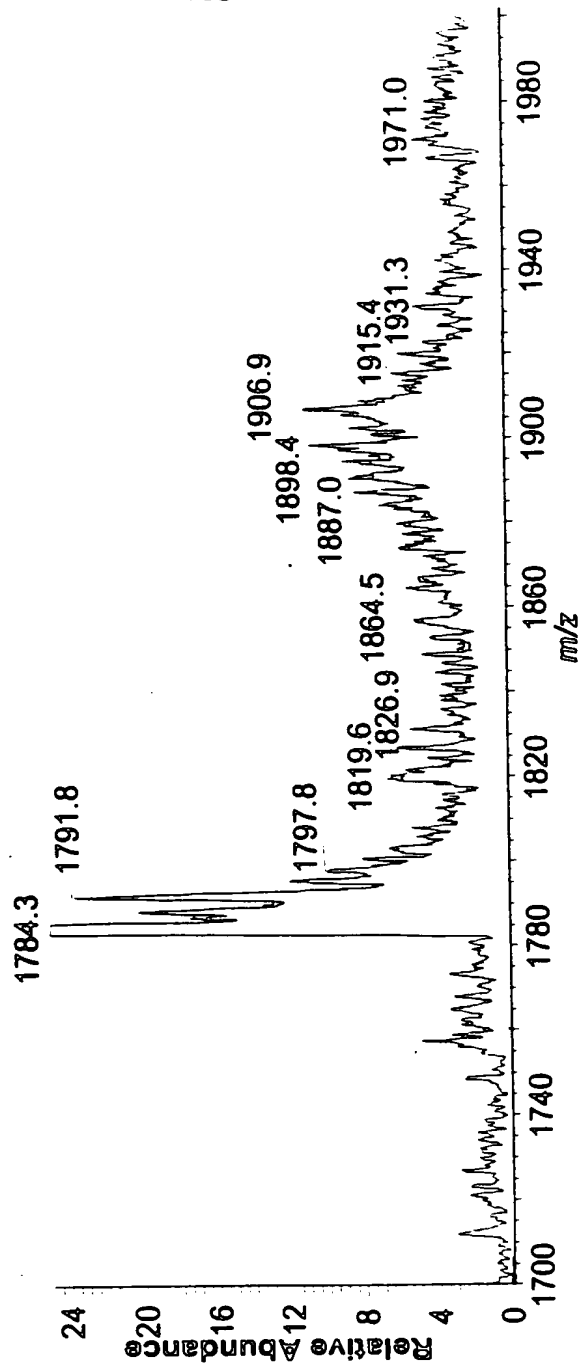


Figure 42B

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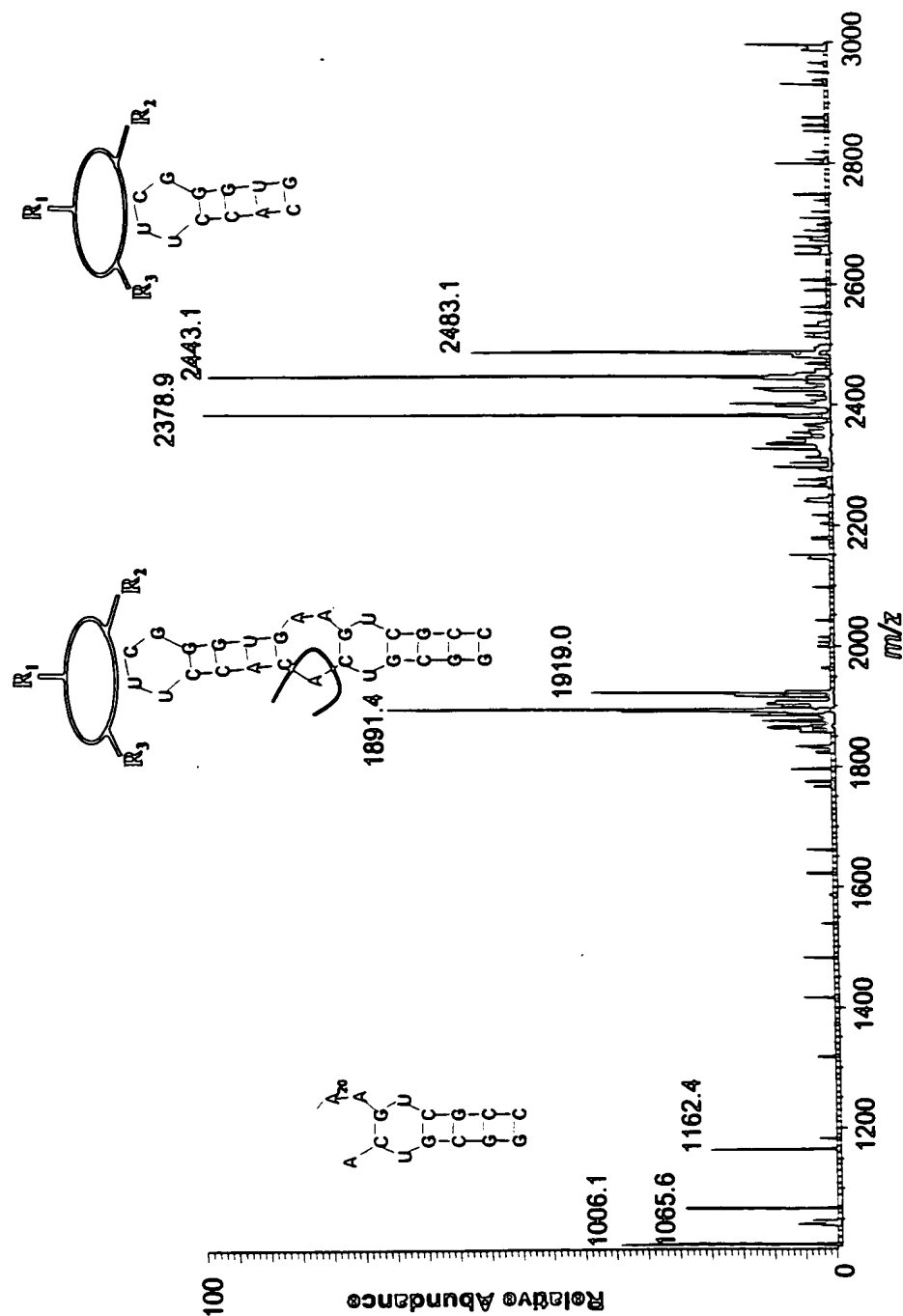


Figure 43

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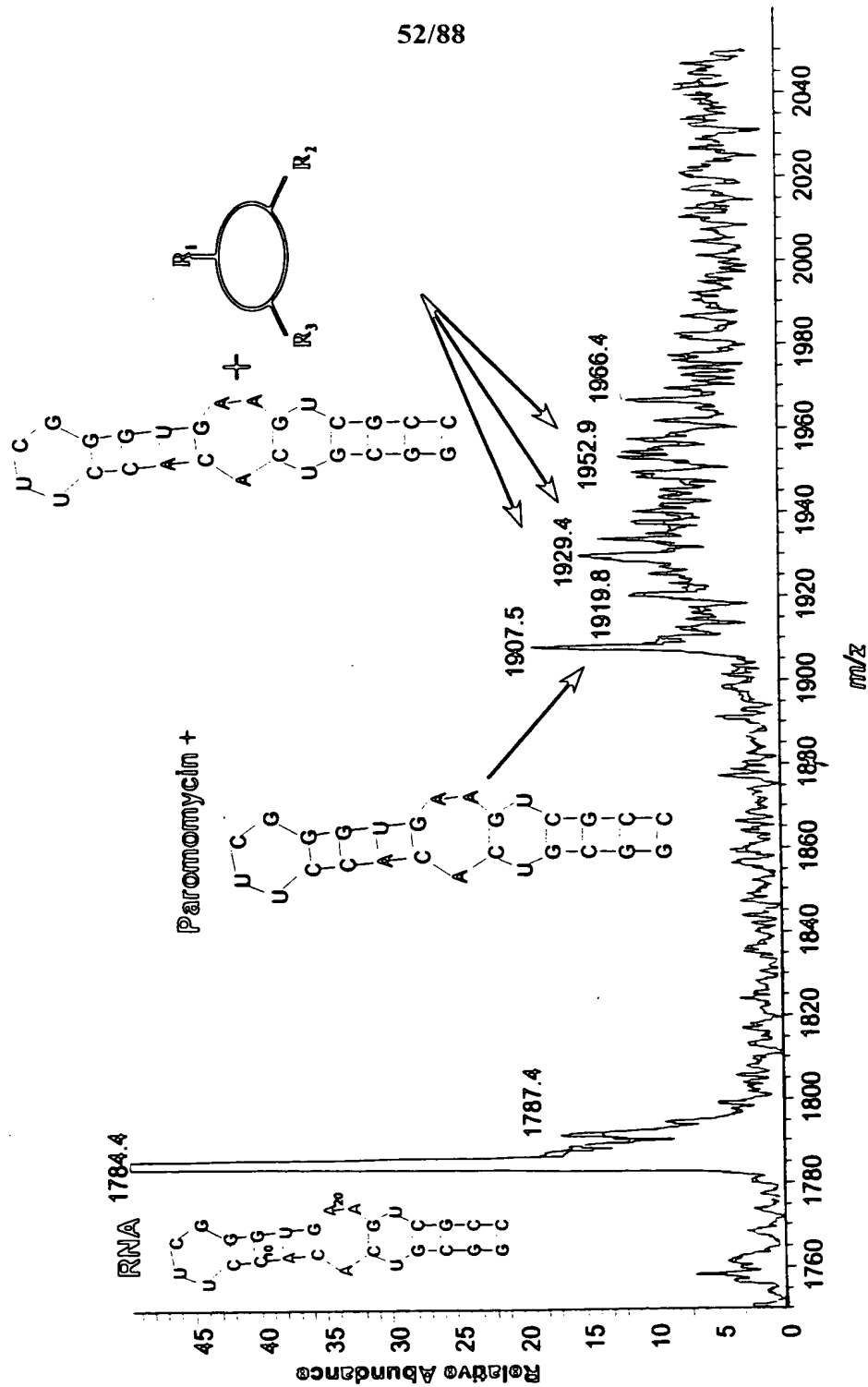


Figure 44

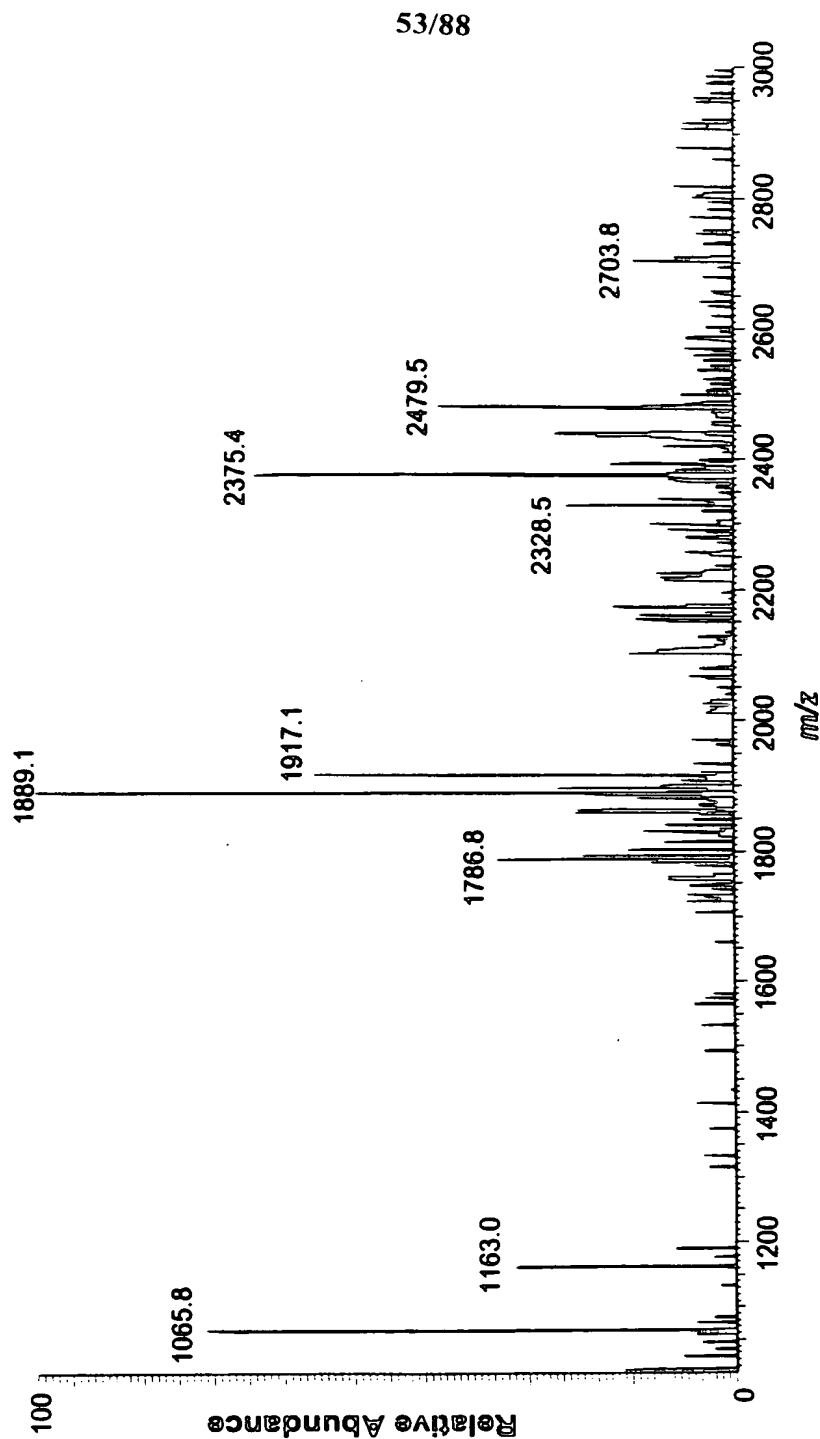


Figure 45



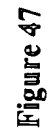




Figure 48

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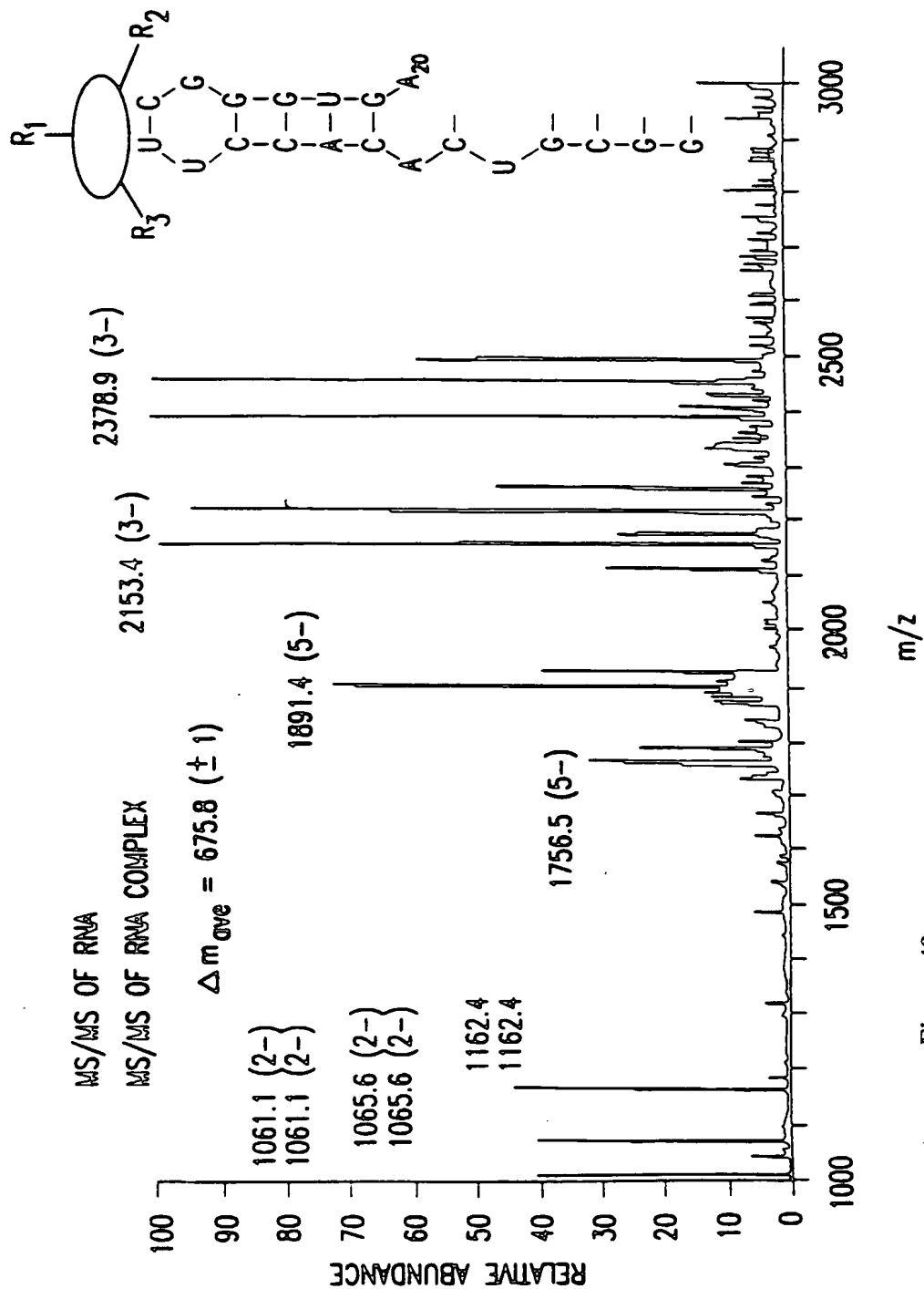


Figure 49

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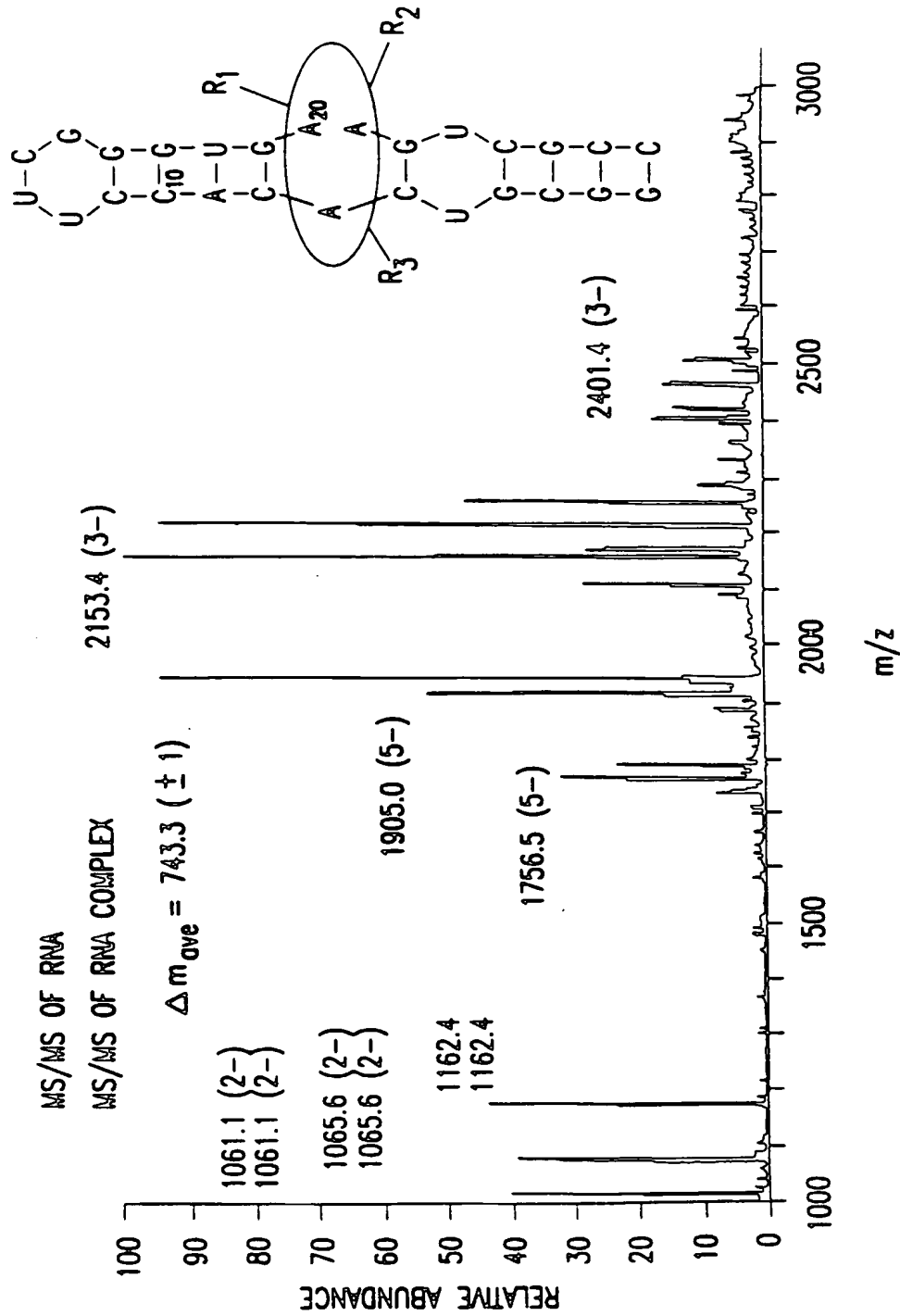


Figure 50



Figure 51

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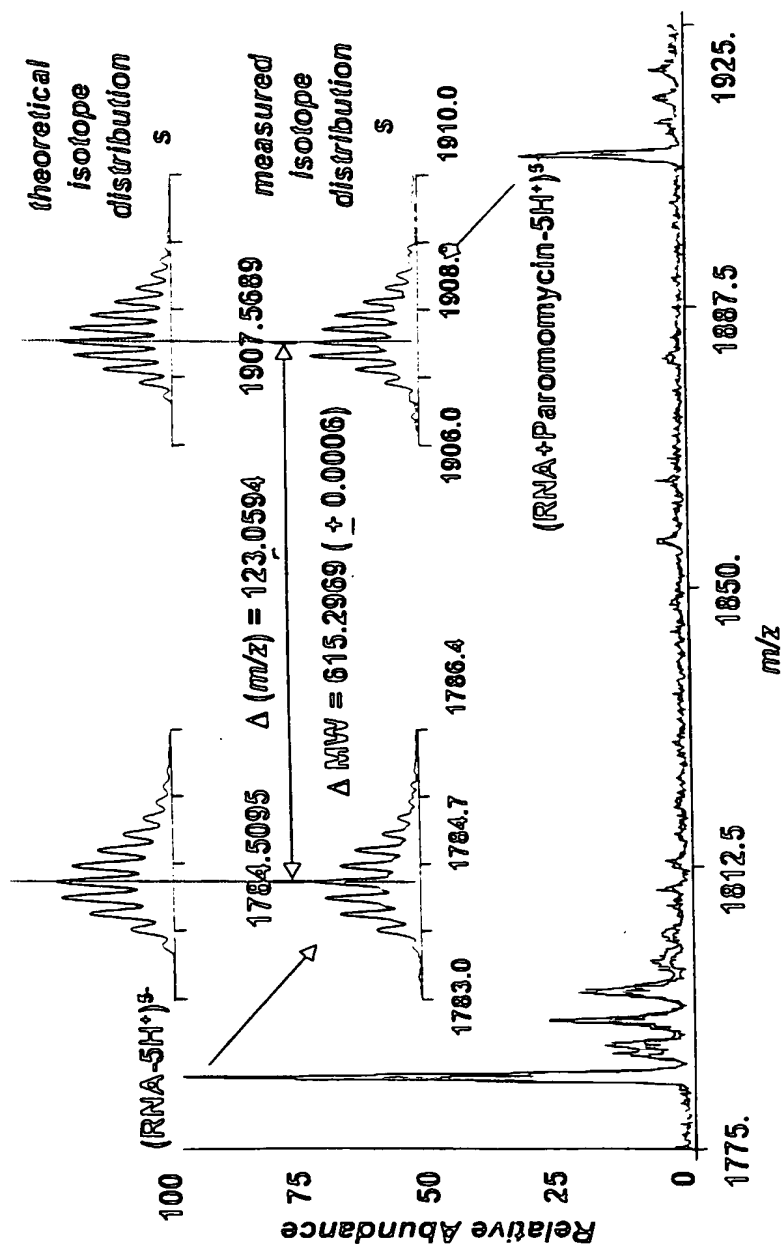
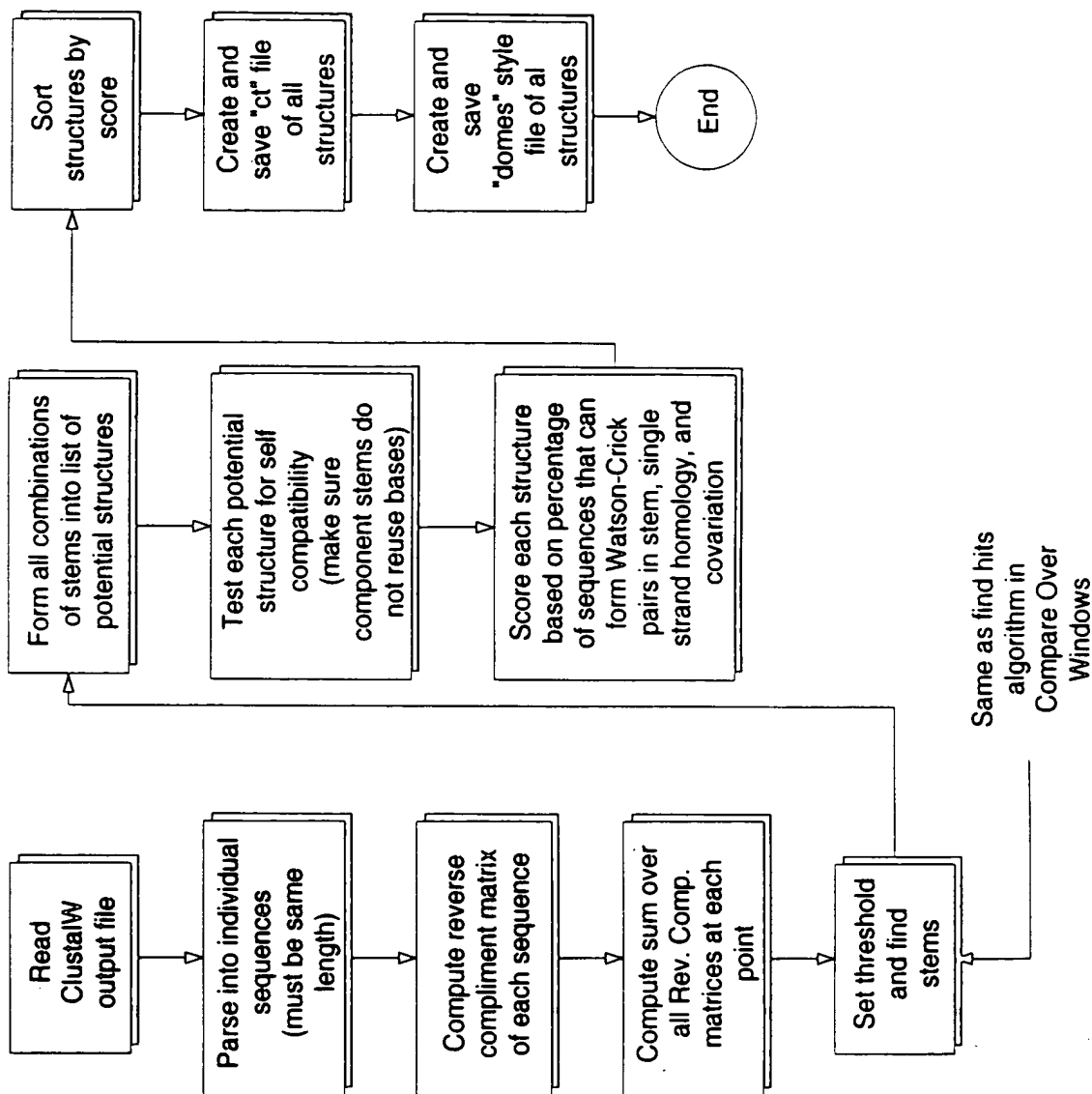


Figure 52

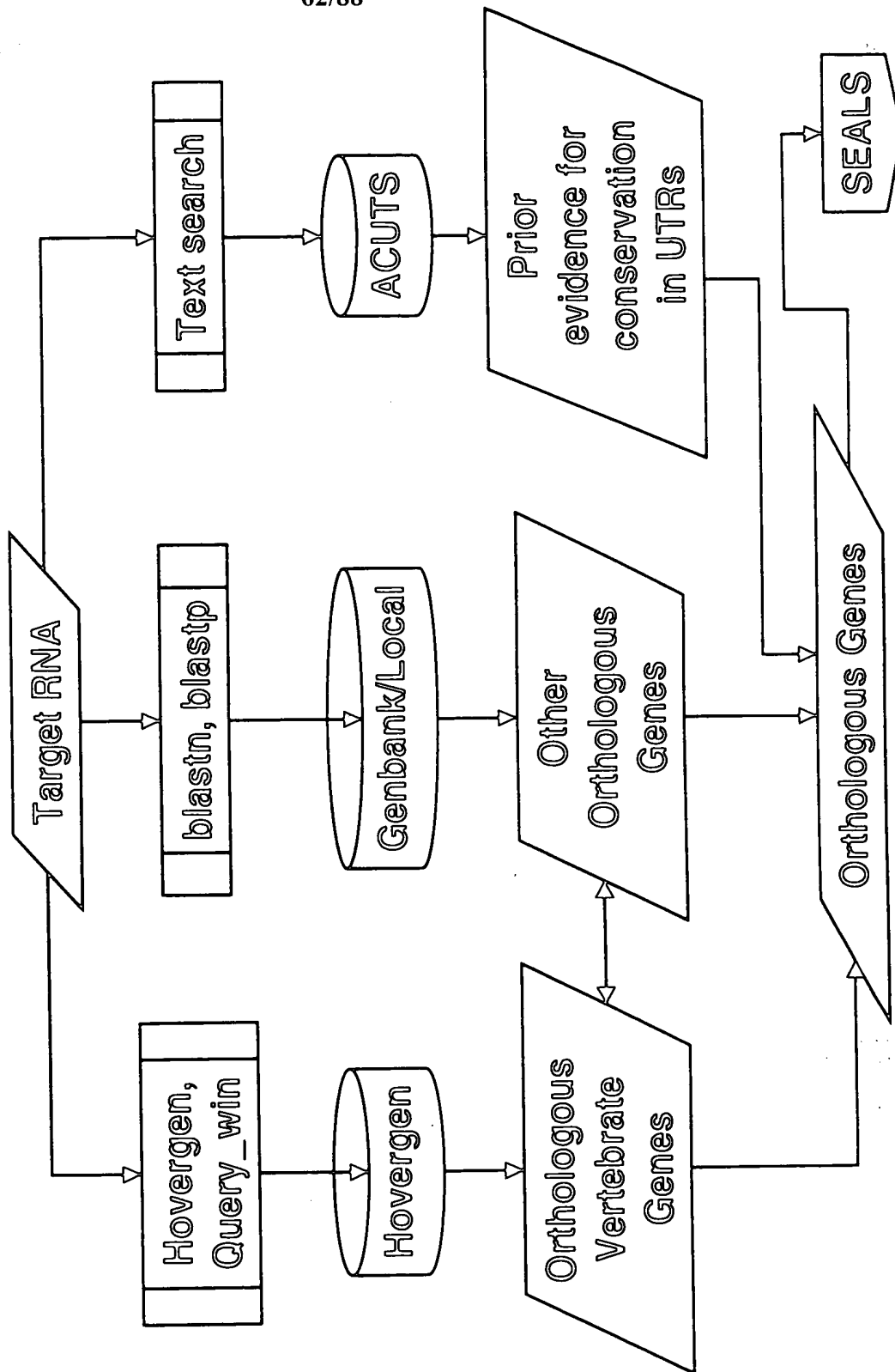
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Figure 53



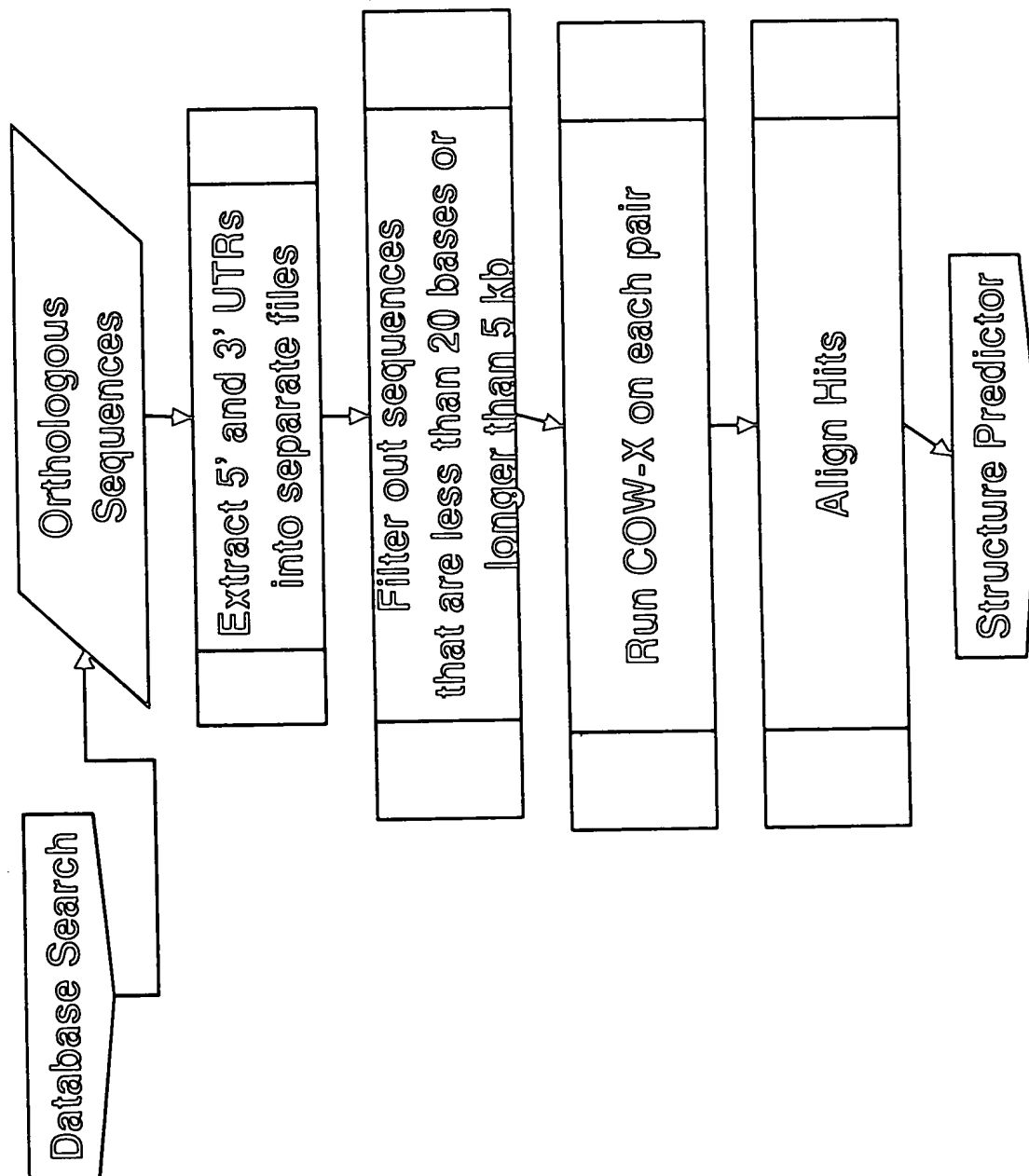
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Figure 54



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Figure 55



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Figure 56

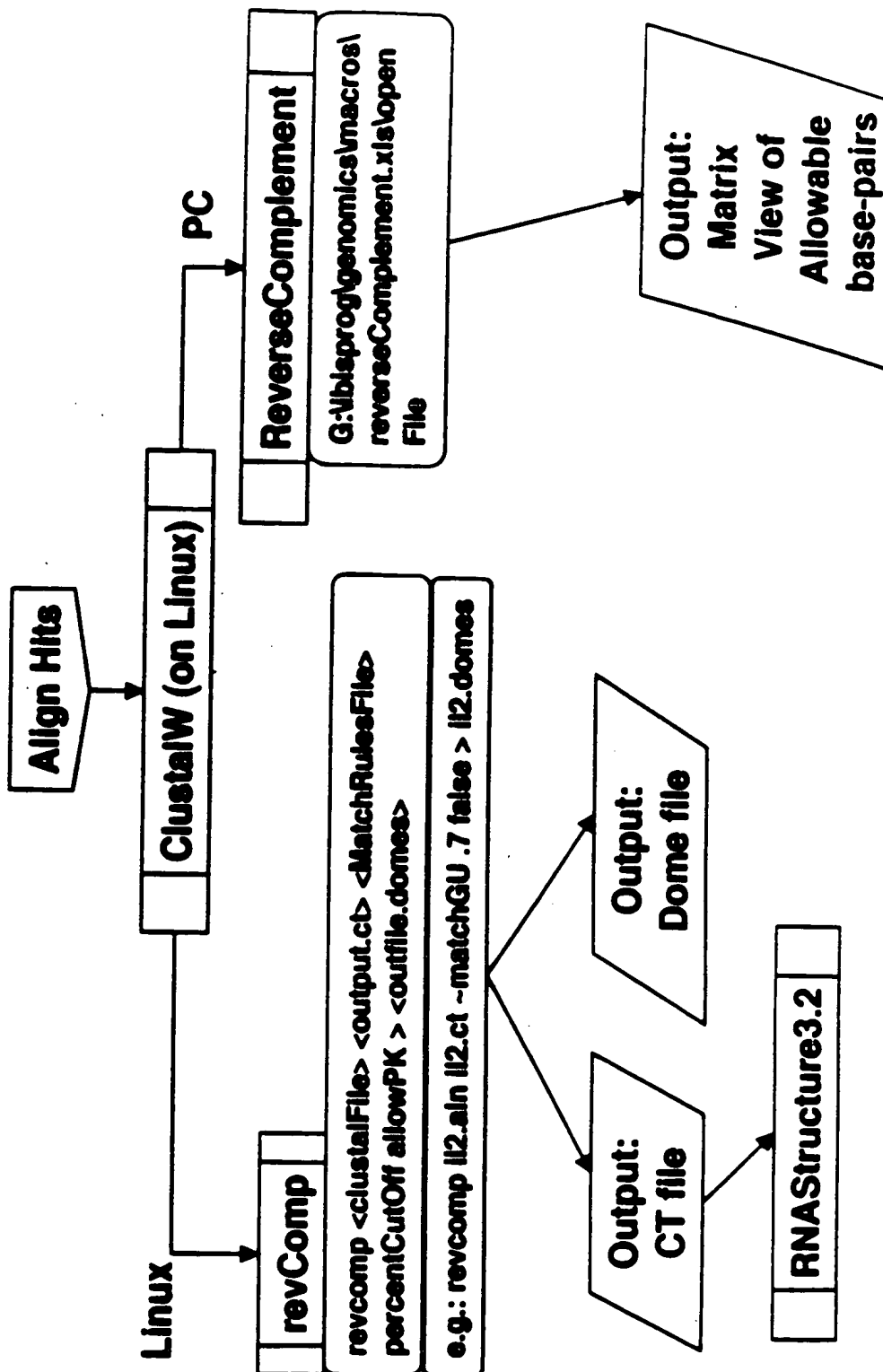


Figure 57

Score: 165.0

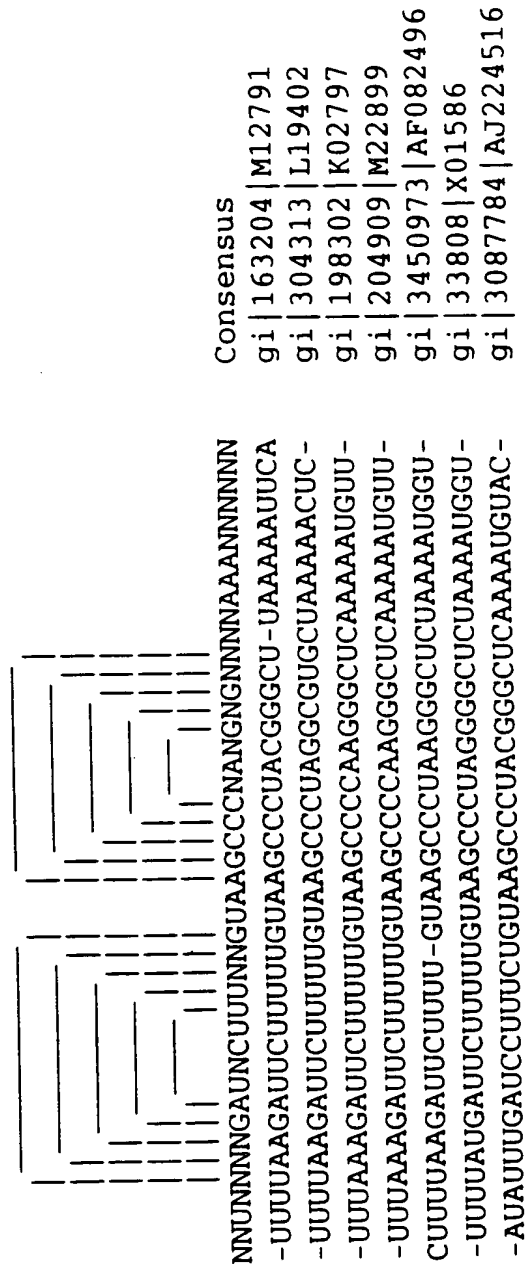


Figure 58

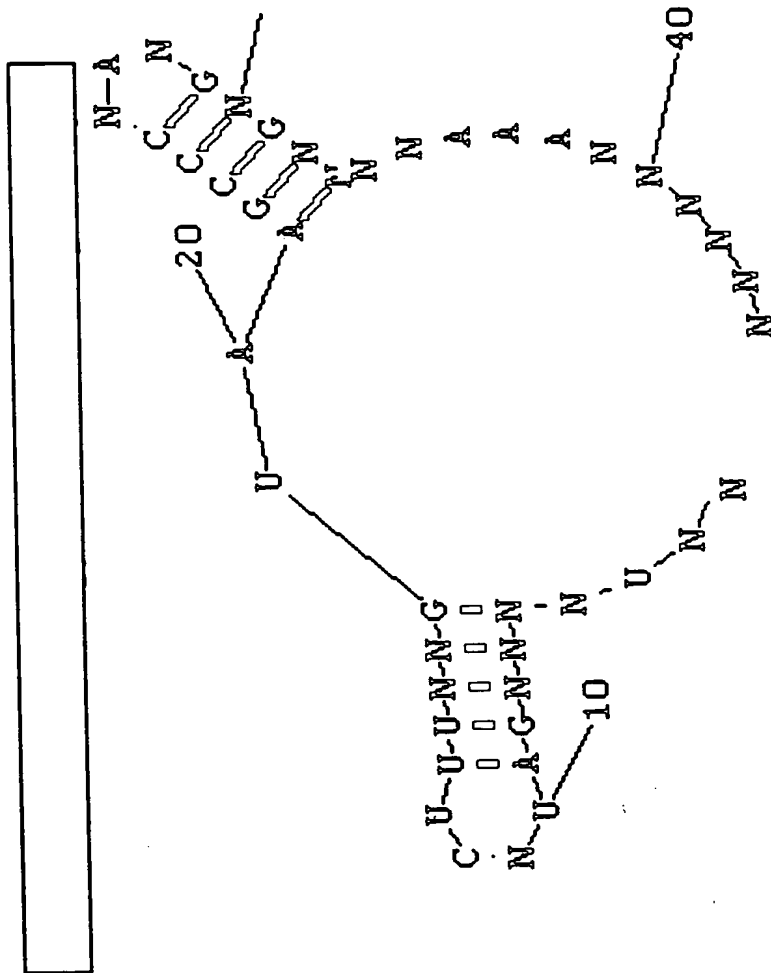
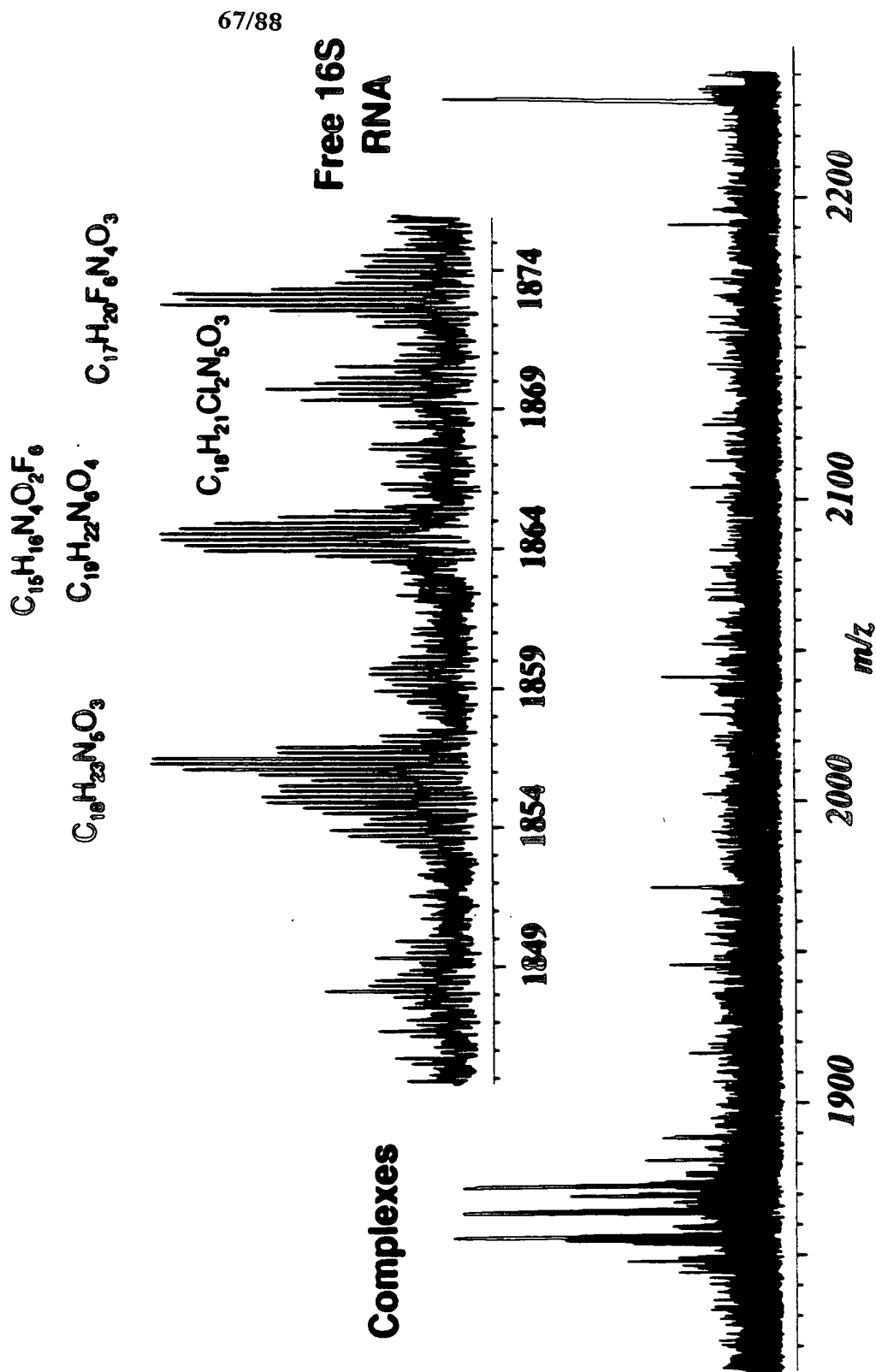


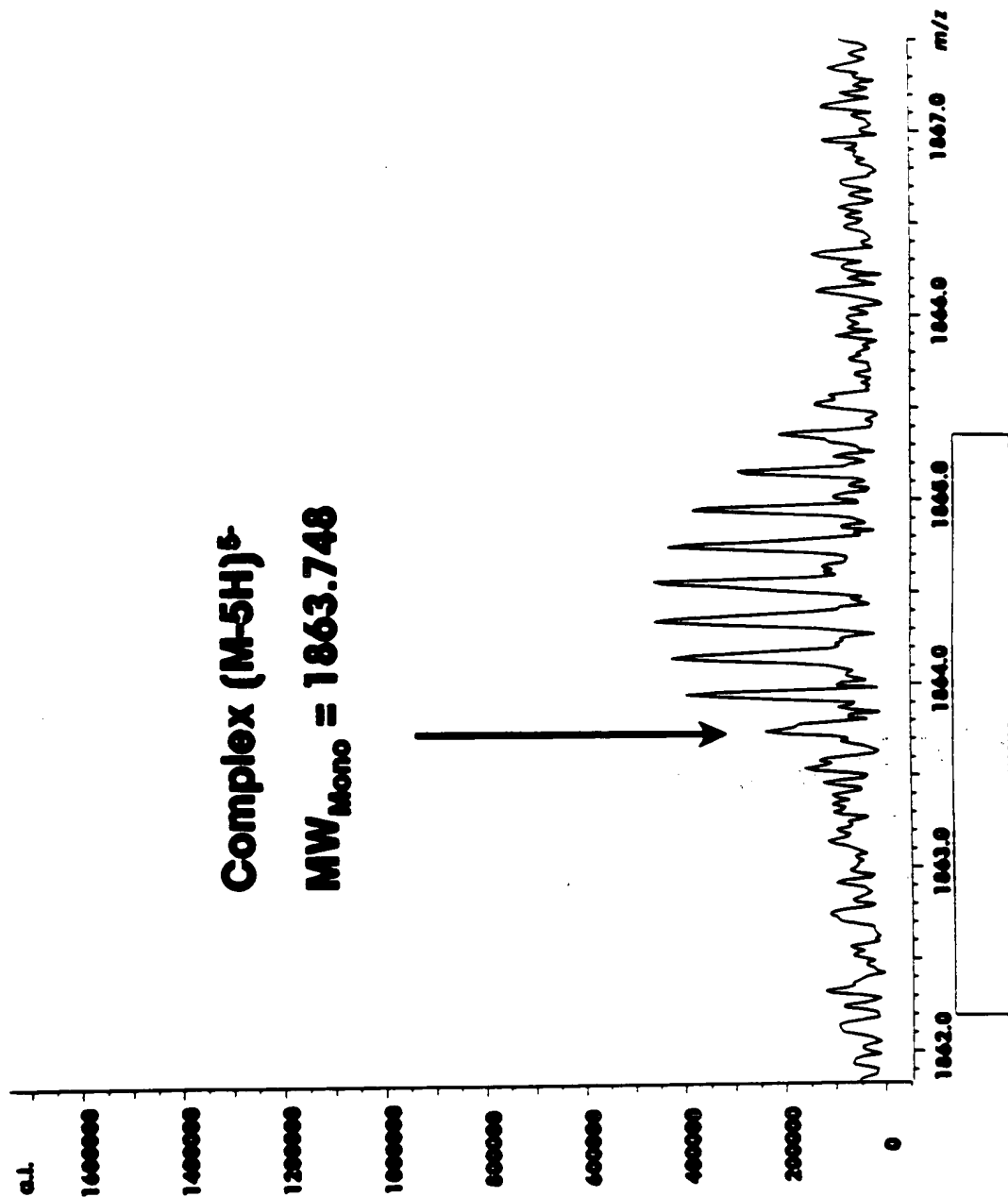
Figure 59

MASS of 60-Member Ibis Library Against 16S A-site RNA



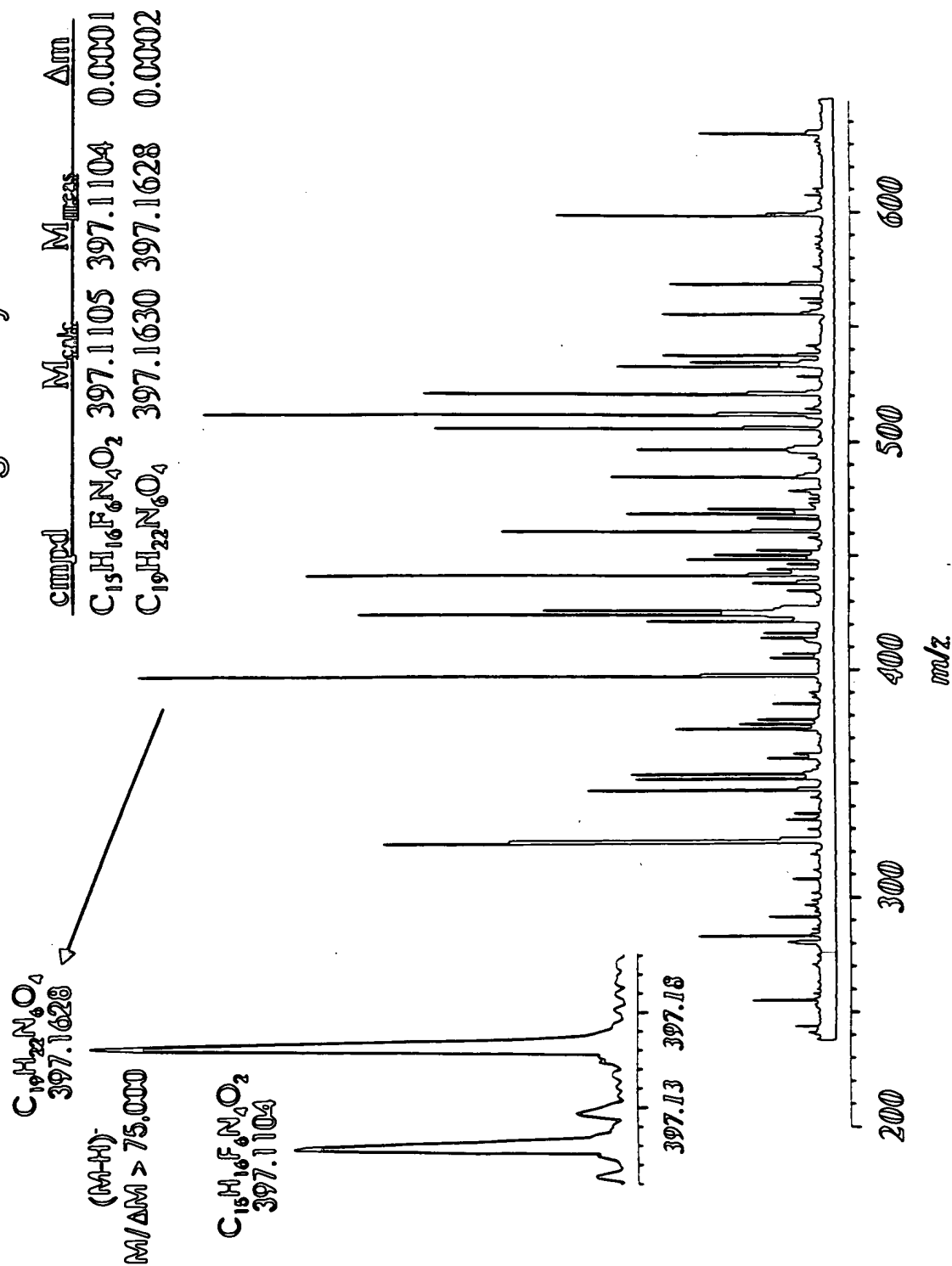
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Figure 60
MASS of 60-member Library against 16S A-site Model



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Figure 61
 FT-ICR MS of Starting Library



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Figure 62
Compound Identification from a 60-member
Combinatorial library with MASS

Complex M_{meas}	9320.300\pm.009 Da
RNA M_{meas}	8922.189\pm.009
ΔM	398.111\pm.009 Da

$C_{15}H_{16}N_4O_2F_6$	398.117 Da
$-C_{19}H_{22}N_6O_4$	----- 998.163 -

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Figure 63
 Elemental Composition Constraints

Measured Mass: 615.2969

Mass Tolerance: 1.0 ppm

Charge: 0

Element Min. atoms Max. atoms

¹² C	12	30
¹ H	23	60
¹⁶ O	7	20
¹⁴ N	3	20

Possible Elemental Compositions:

Calc. Mass Error Molecular Formula

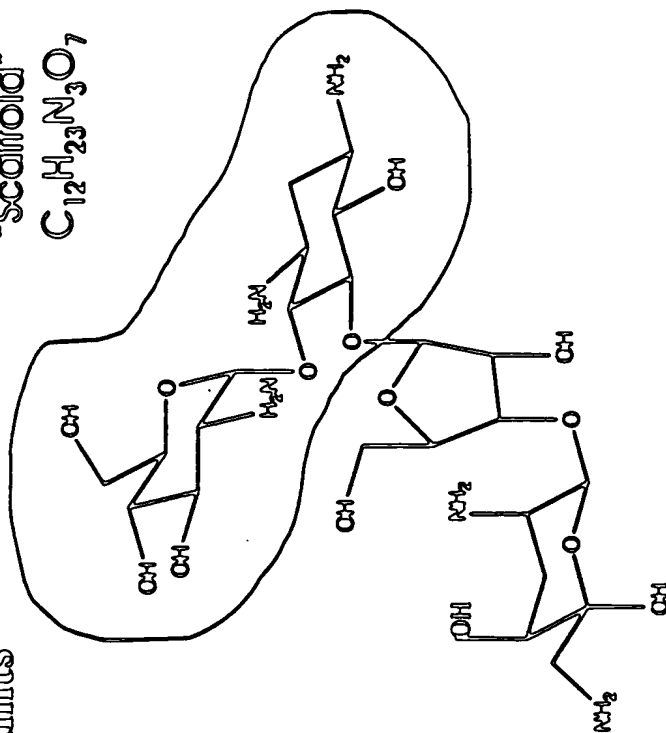
(amu) (ppm)

615.296291	-0.98	¹⁶ O ₄ ¹⁴ N ₉ ¹² C ₂₁ ¹ H ₃₃
615.296298	0.98	¹⁶ O ₉ ¹⁴ N ₁₂ ¹² C ₂₂ ¹ H ₃₉
615.296305	0.97	¹⁶ O ₁₄ ¹⁴ N ₅ ¹² C ₂₃ ¹ H ₄₅
615.296808	-0.15	¹⁶ O ₁₅ ¹⁴ N ₁₇ ¹² C ₈ ¹ H ₄₁
615.296815	-0.14	¹⁶ O ₂₀ ¹⁴ N ₁₀ ¹² C ₉ ¹ H ₄₇



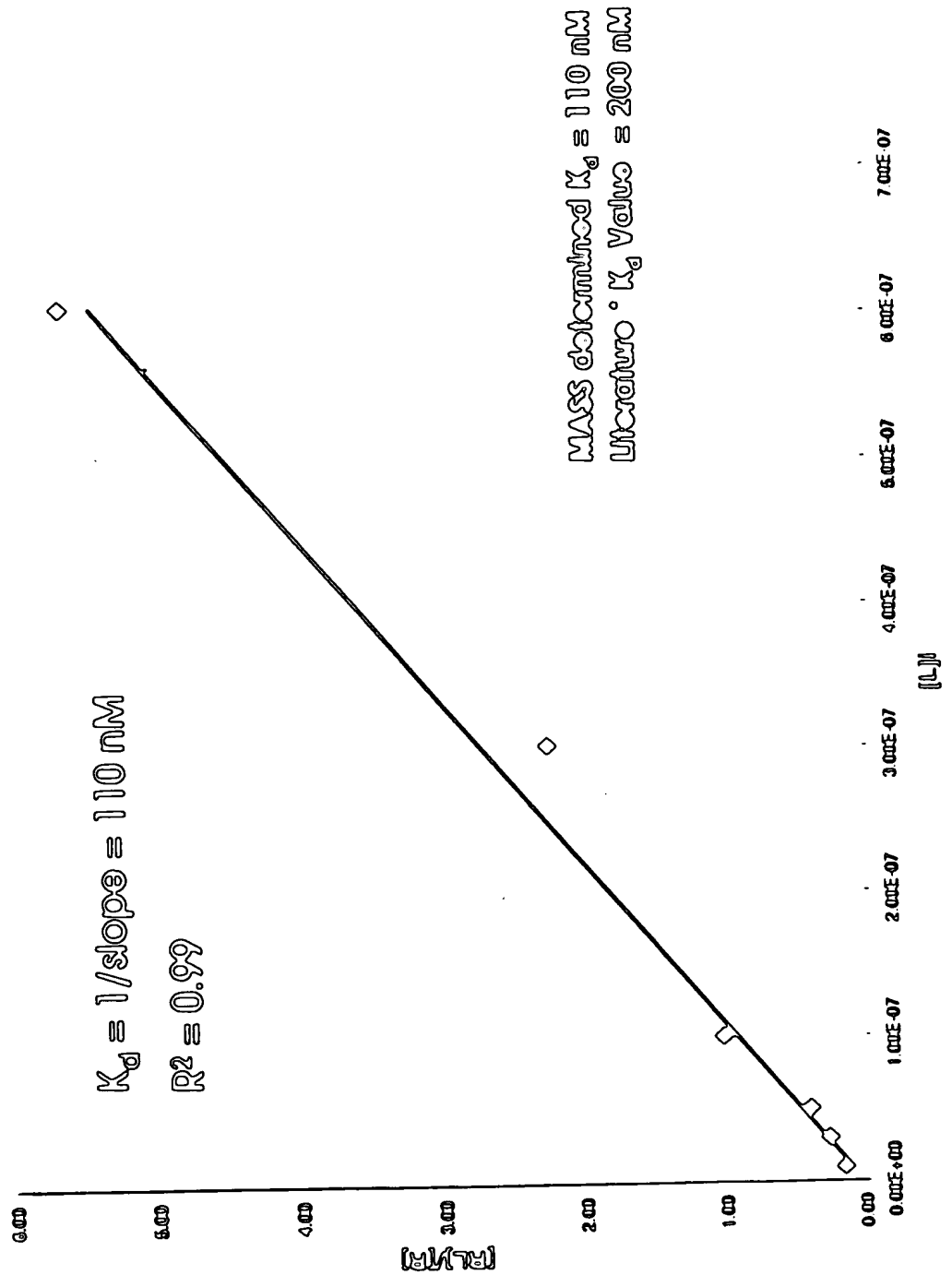
Further constraint by
 elemental
 composition of
 "lofters"
 unintended
 products...

"Scaffold"
 $C_{12}H_{23}N_3O_7$



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Figure 64
 MASS K_d determination for 16S-Paromomycin



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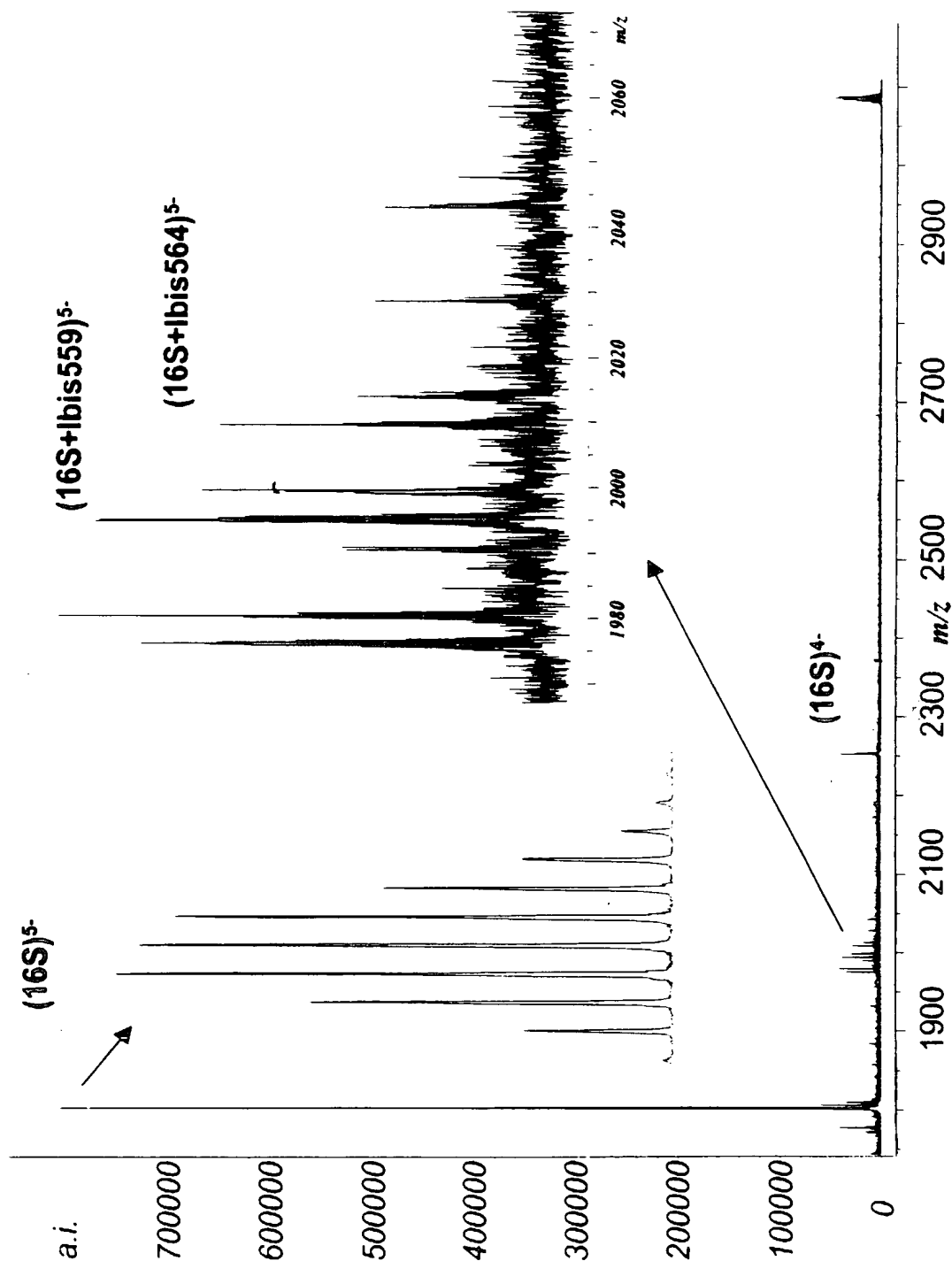


Figure 65

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Figure 66
 MASS Protection Assay

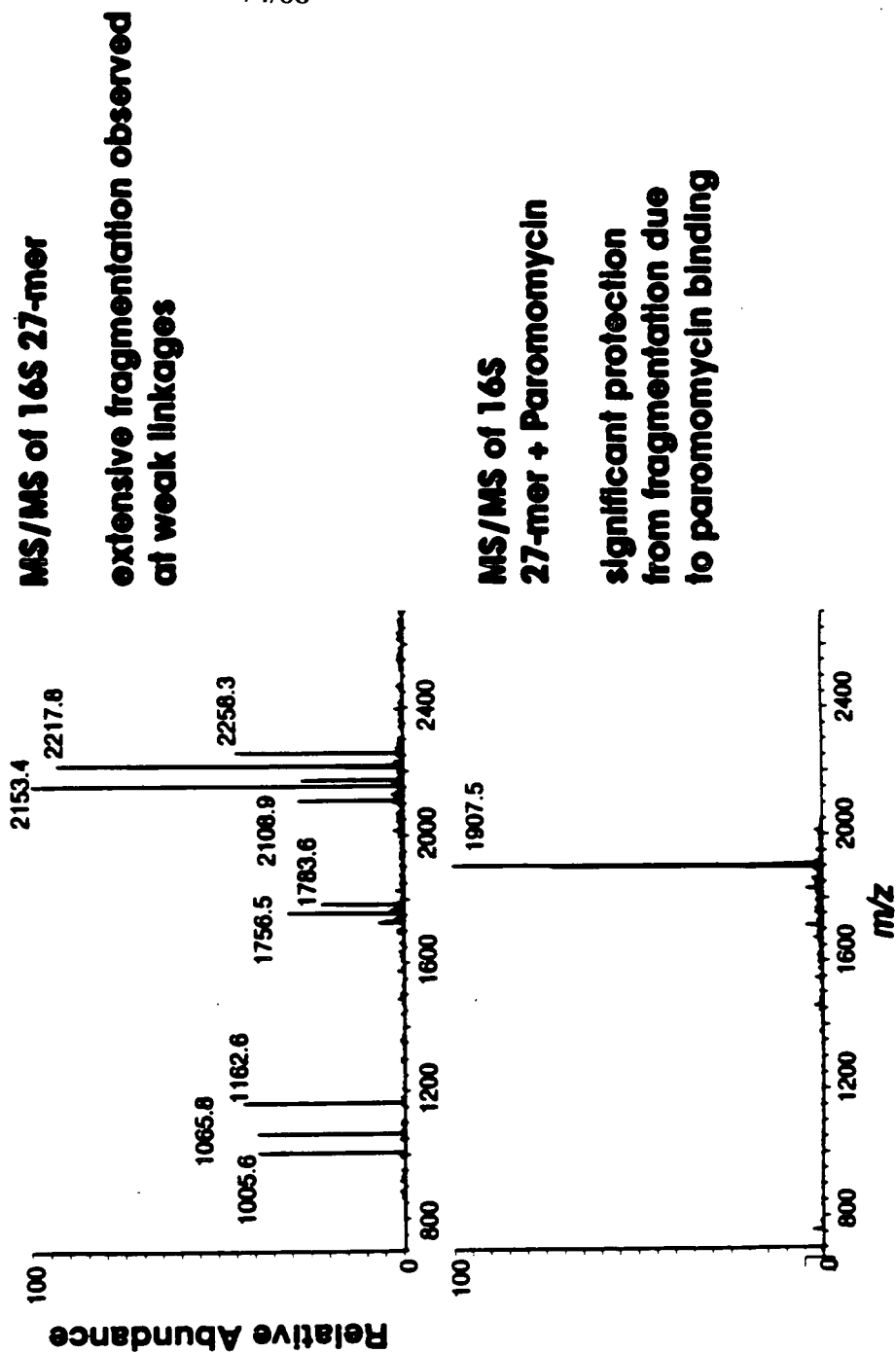
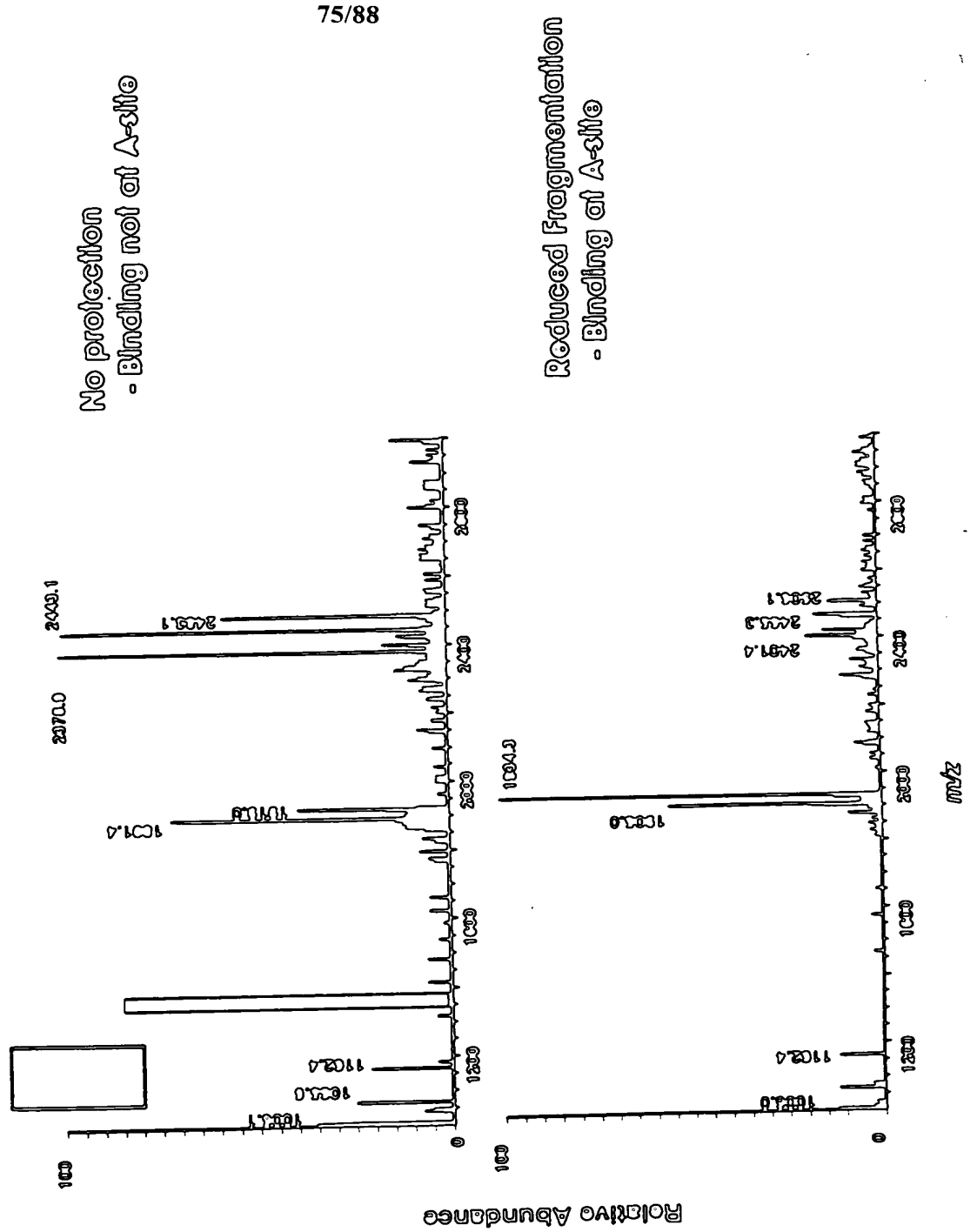
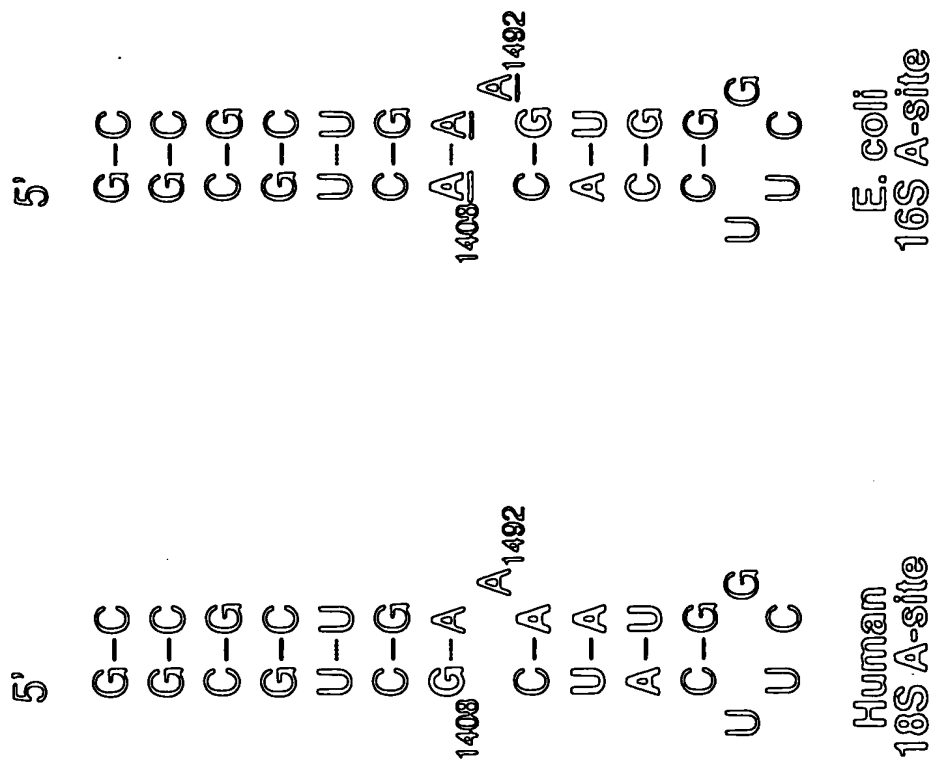


Figure 67
 MASS Protection Assay



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Figure 68
Eukaryotic and Prokaryotic A-Sites
 Aminoglycoside antibiotics bind to
 A-site of decoding region in 16S RNA



$\Delta MW = 15.011 Da$

Figure 69
 Neutral Mass Tag Does Not Affect Ligand Binding

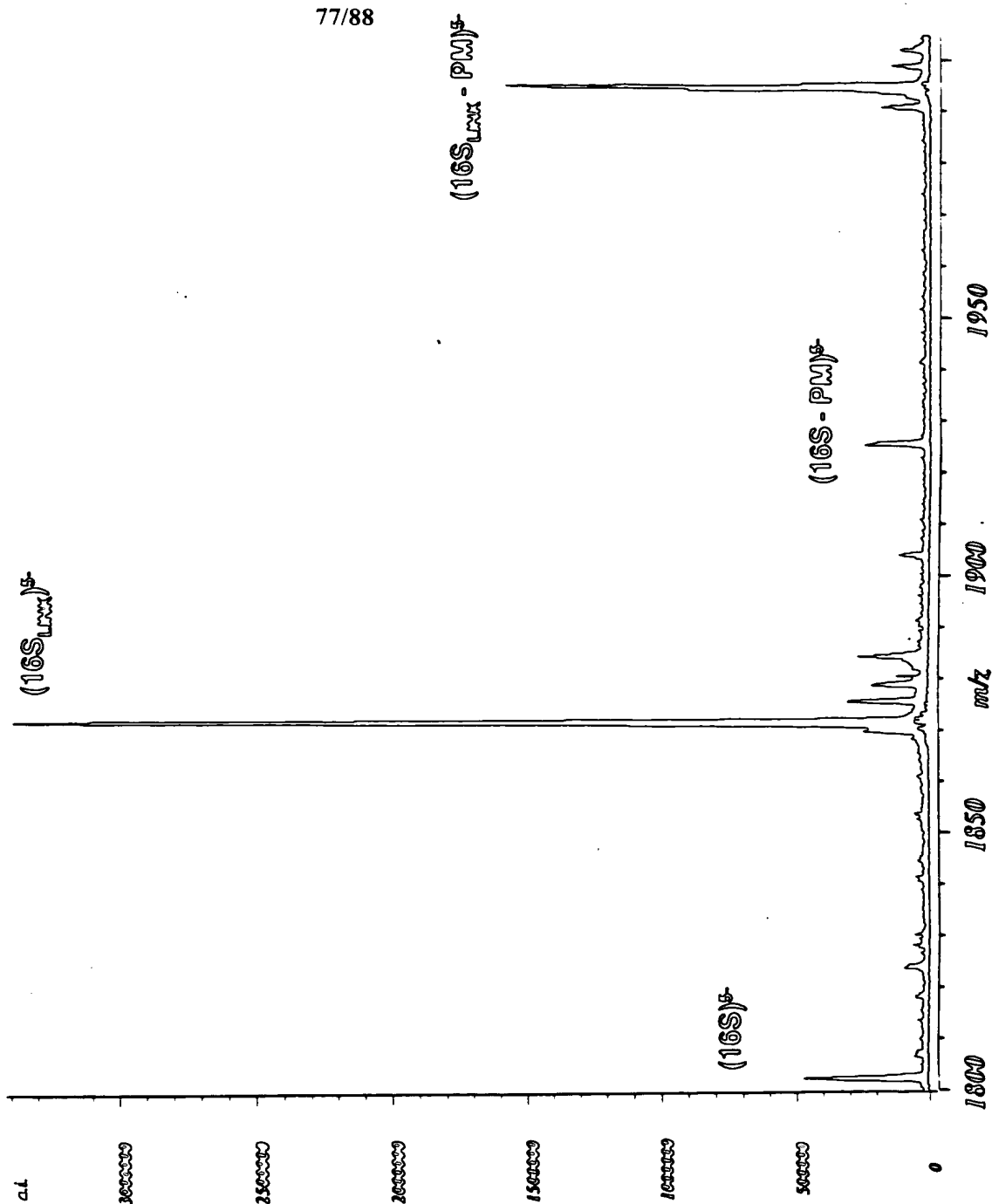


Figure 70



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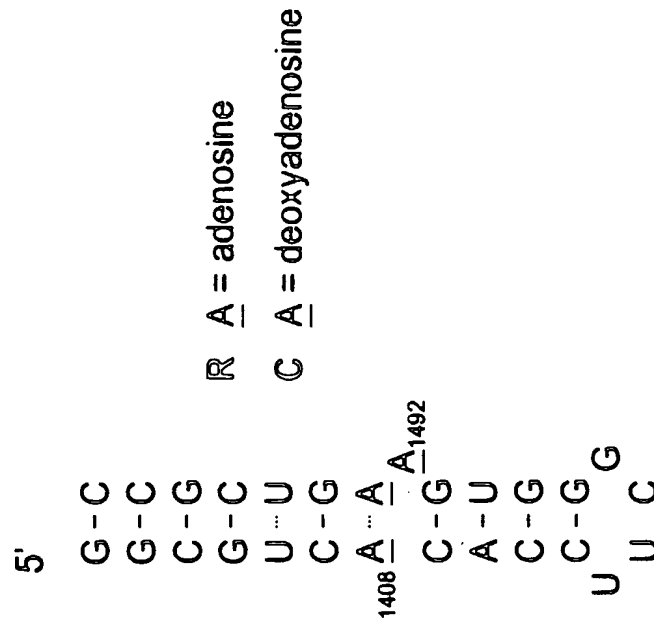
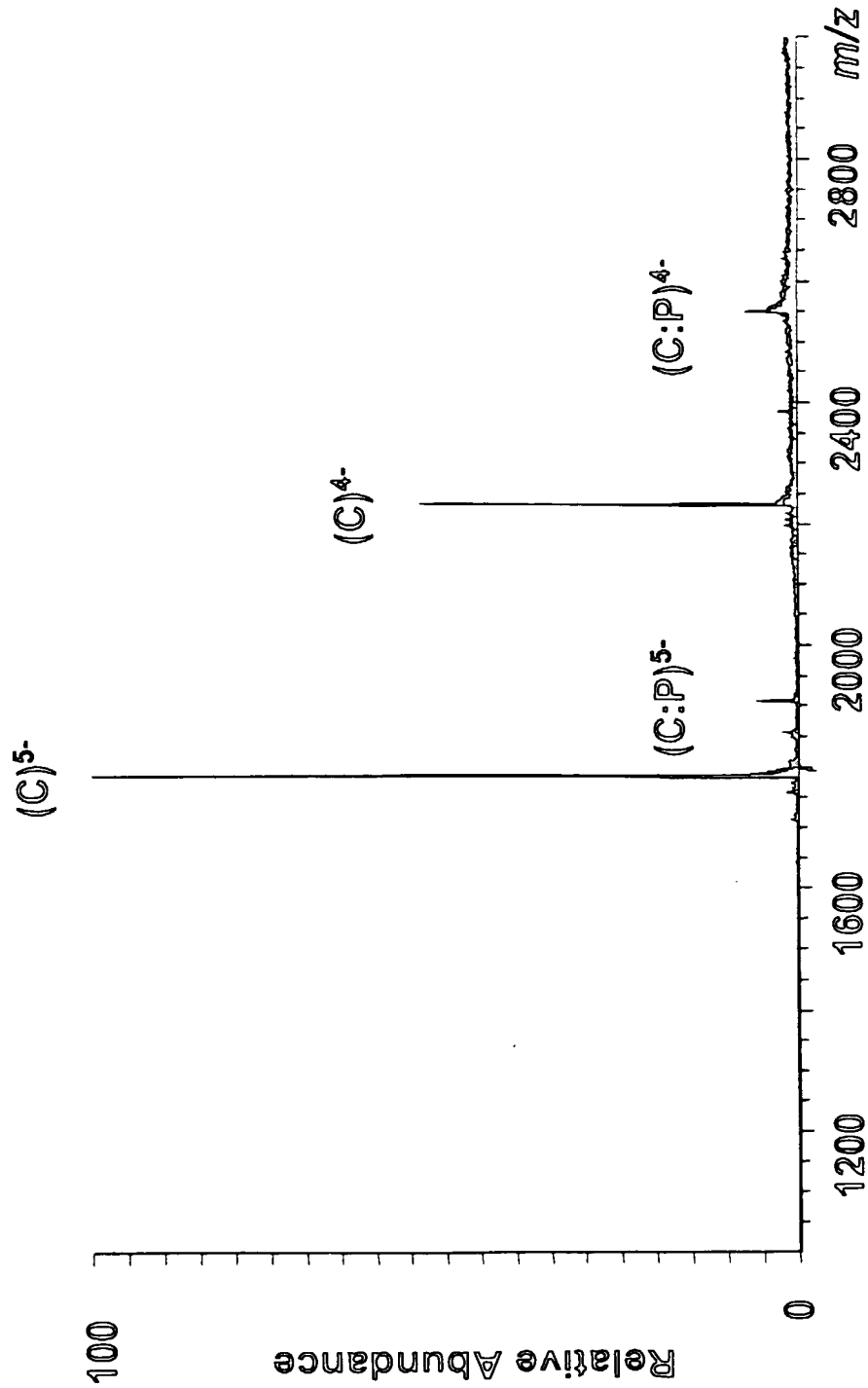


Figure 71

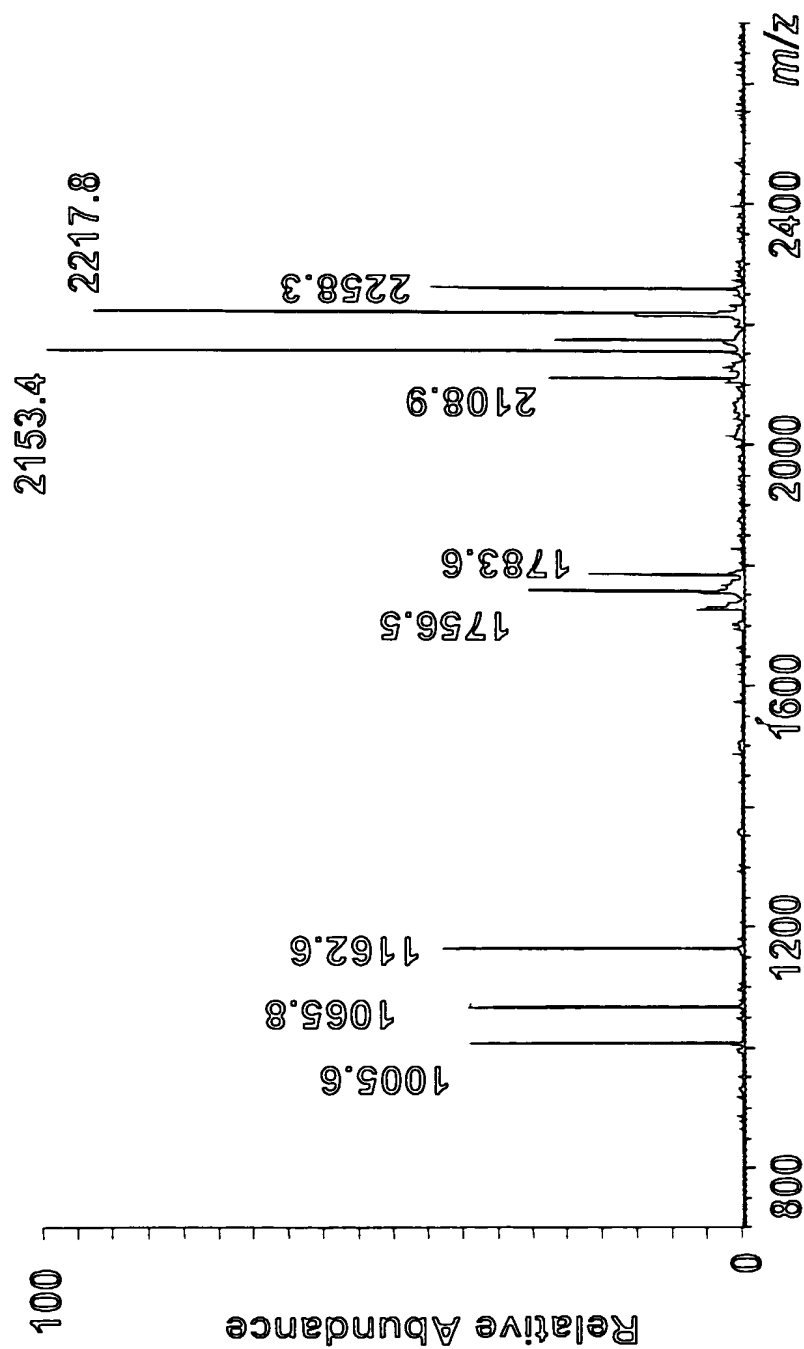
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Figure 72A



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Figure 72B



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Figure 72C

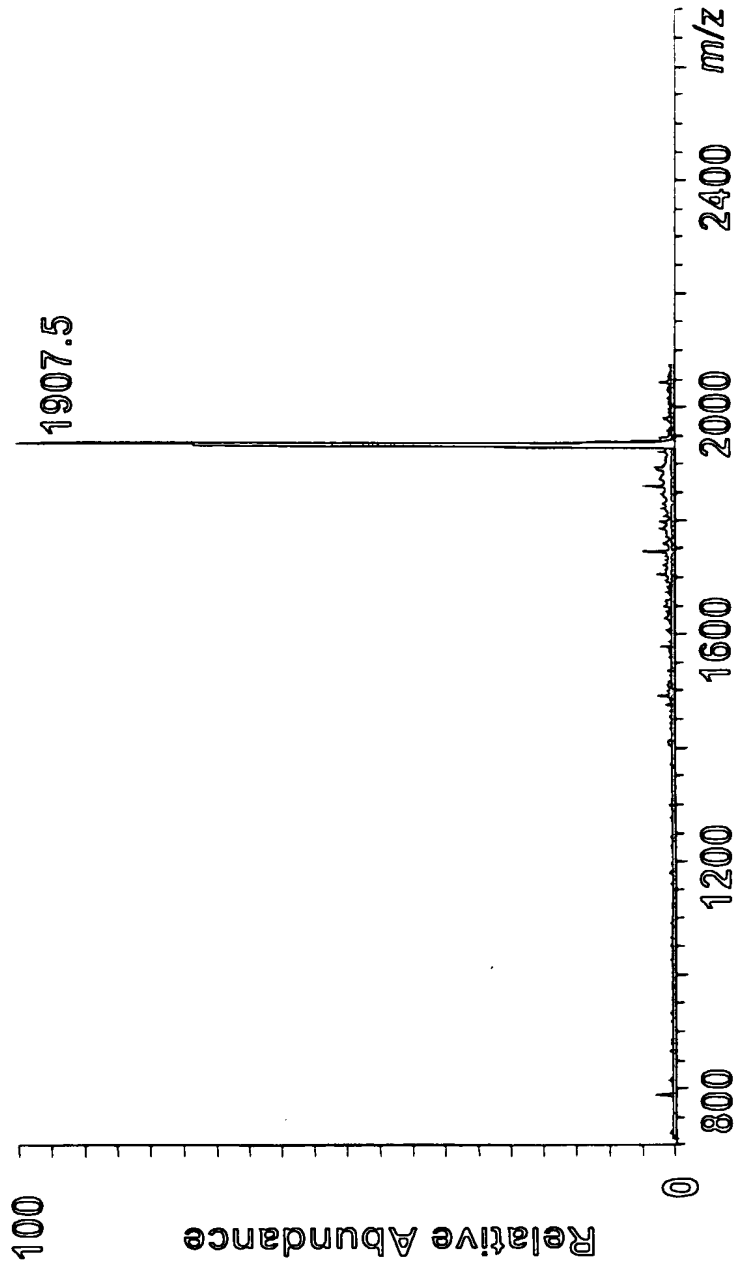
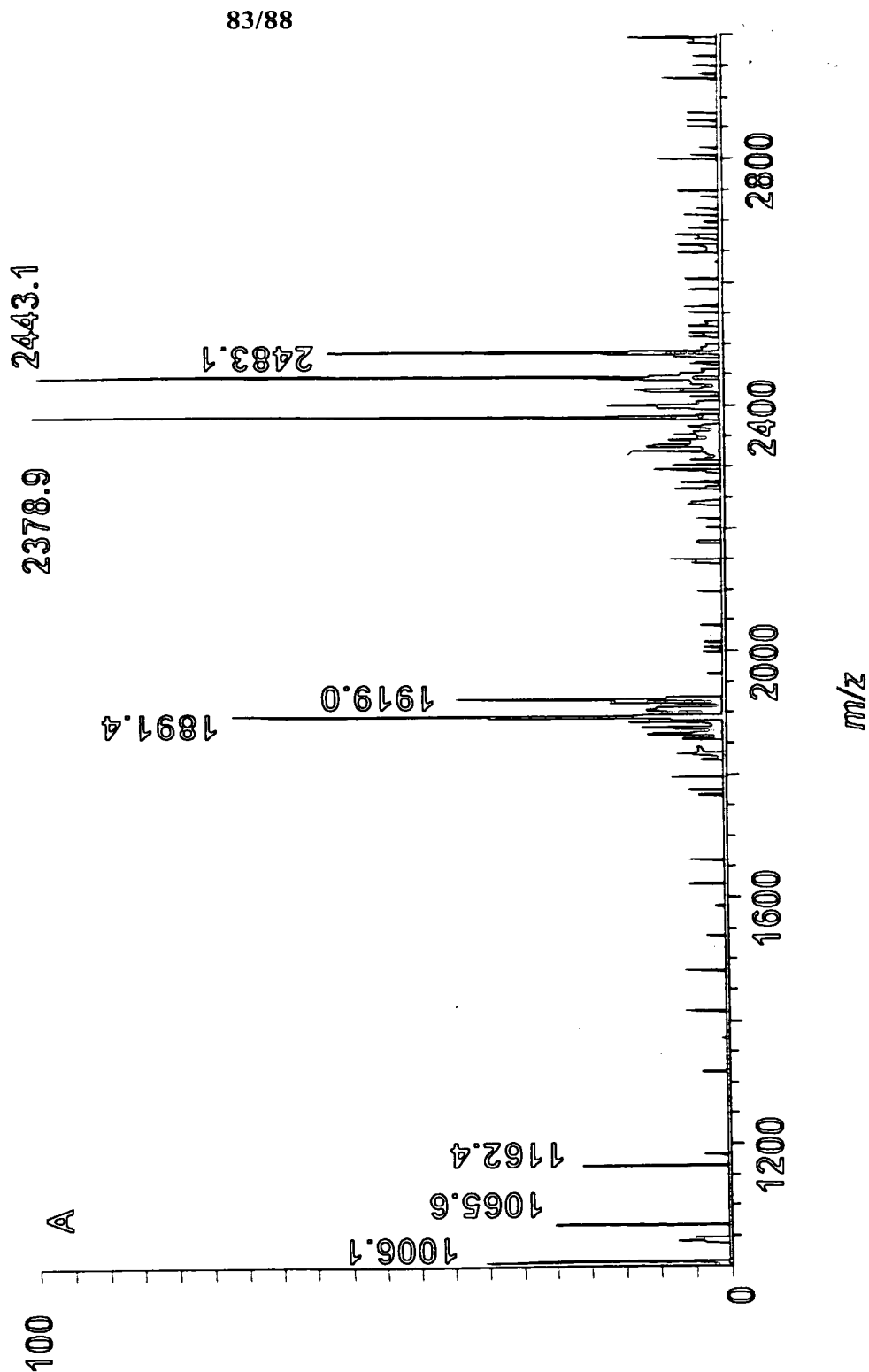
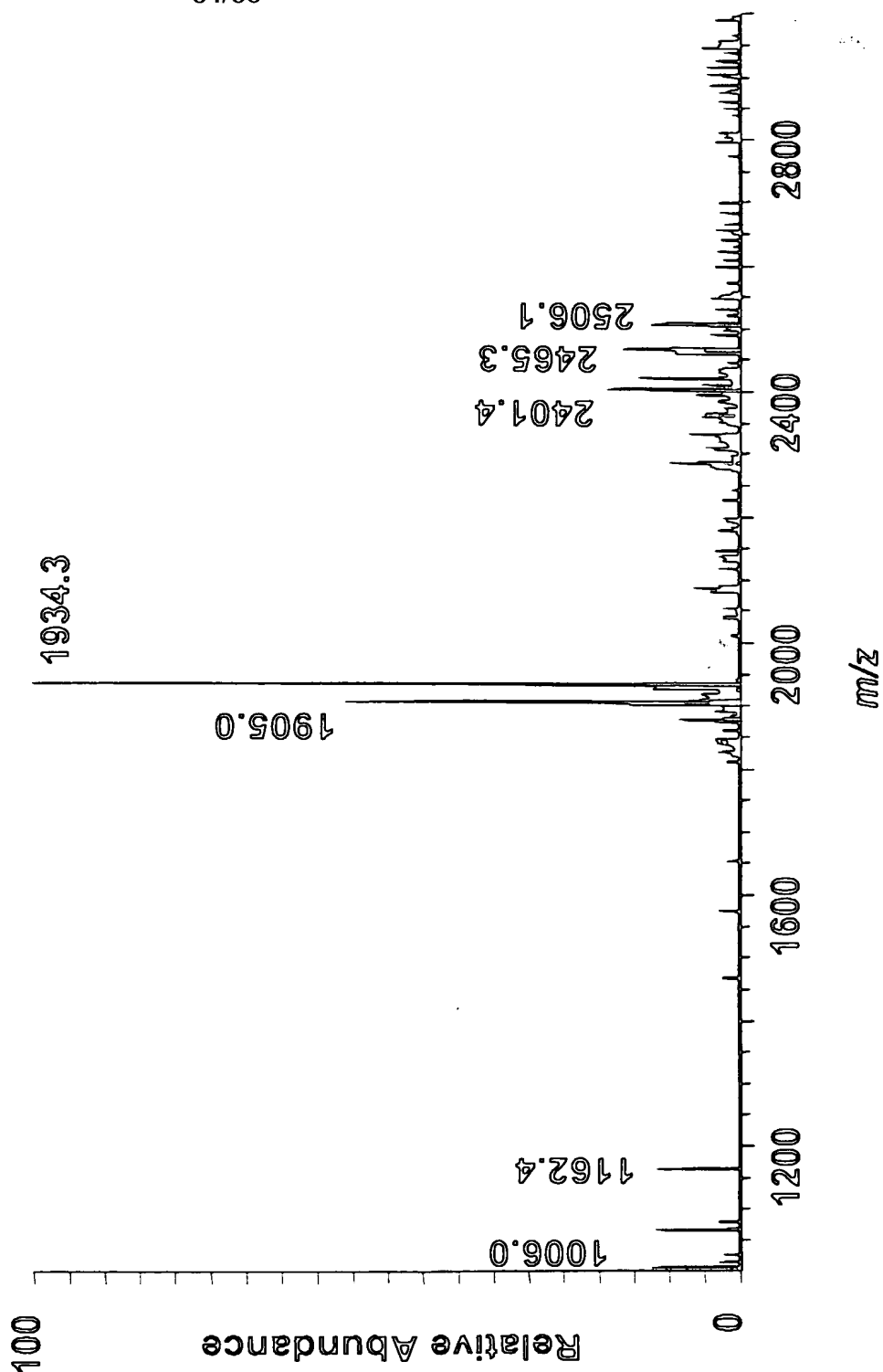


Figure 73A



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Figure 73B



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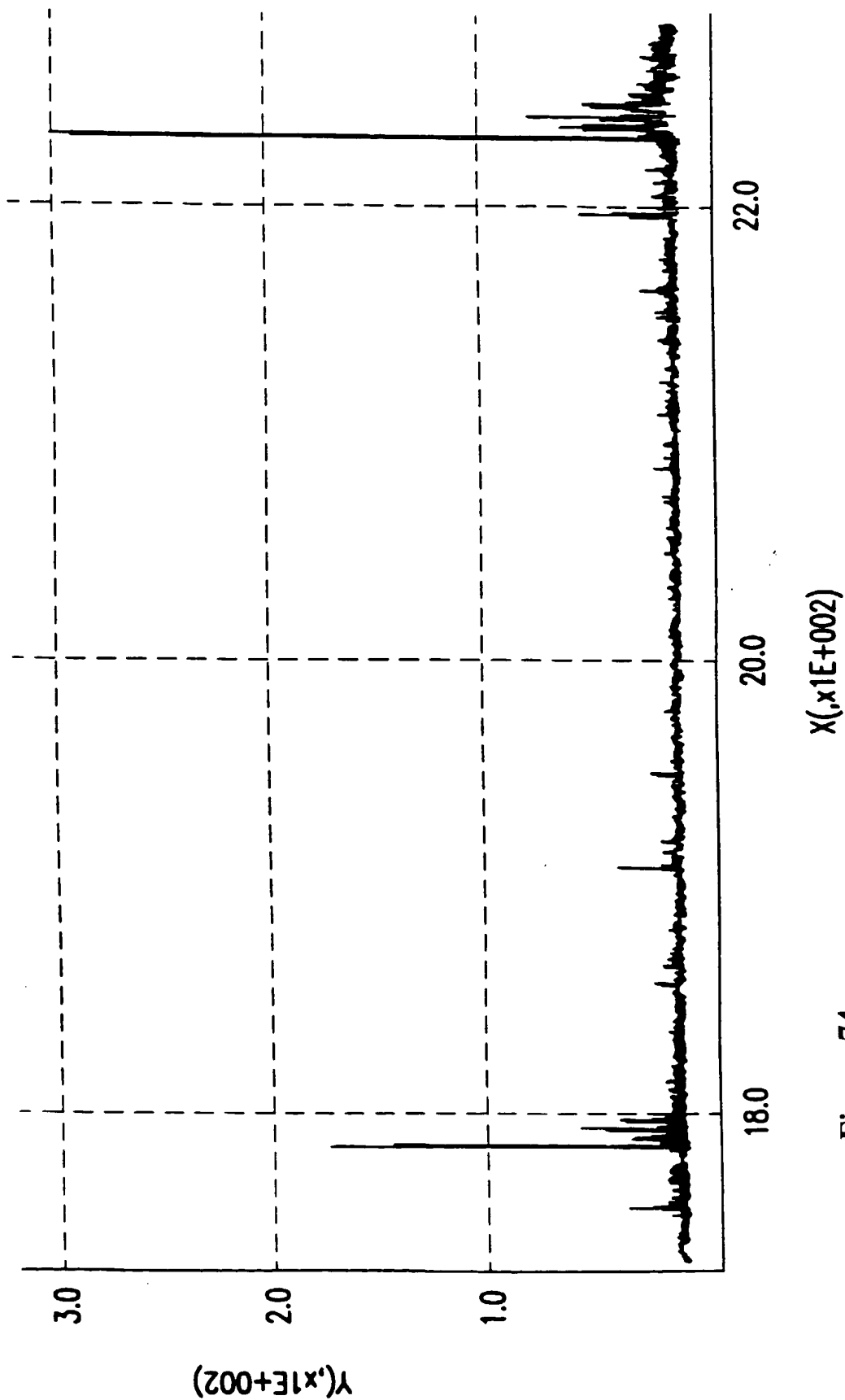
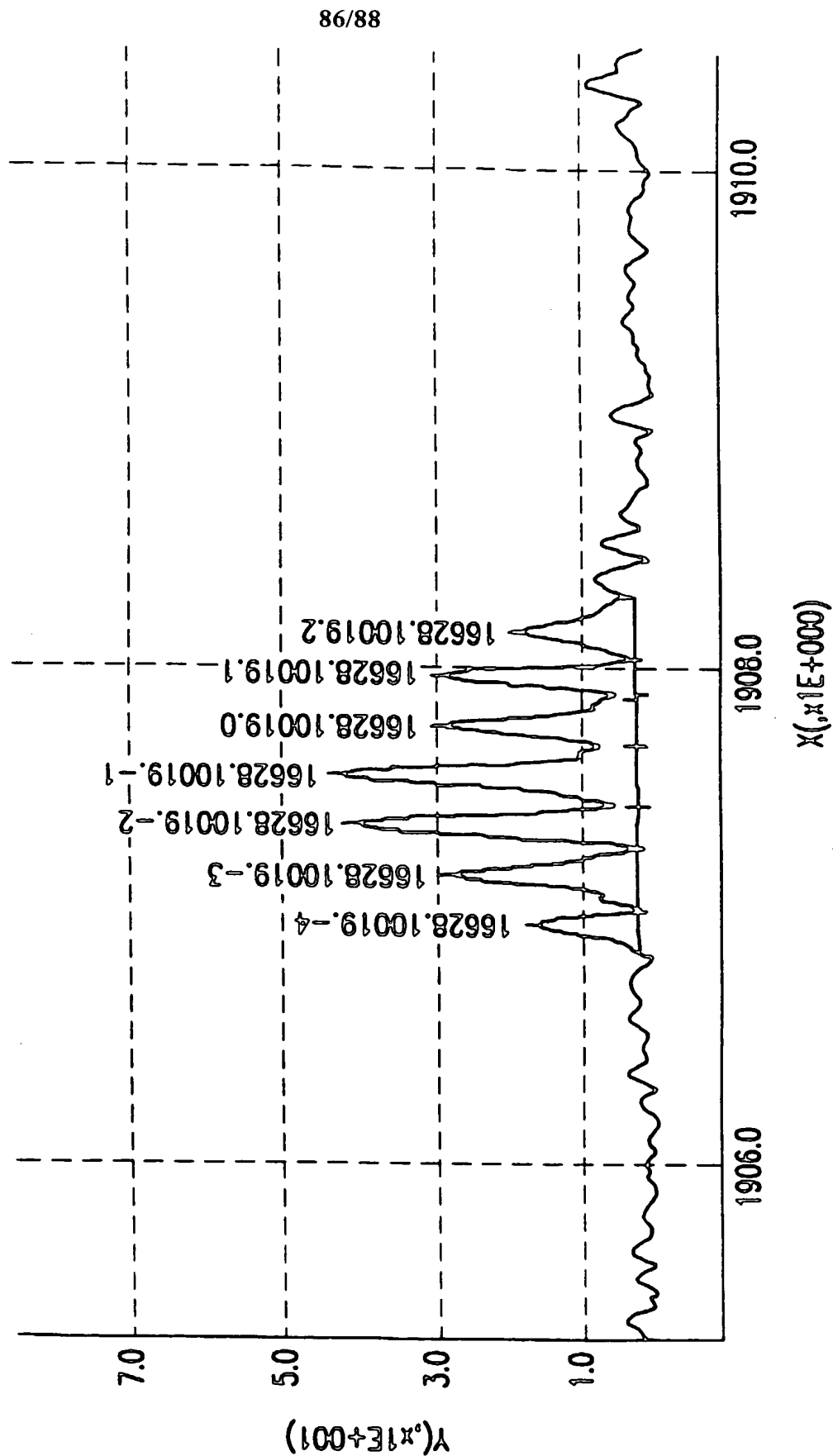


Figure 74

Figure 75



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nr	name	apex	start	stop	height	area
1	16628-1.4	1783.710	1783.635	1783.834	14.55	1.63
2	16628-1.3	1783.909	1783.834	1783.972	60.04	5.15
3	16628-1.2	1784.109	1784.021	1784.184	115.60	11.14
4	16628-1.1	1784.308	1784.233	1784.383	167.34	15.89
5	16628-1.0	1784.508	1784.433	1784.620	133.94	14.74
6	16628-1.1	1784.707	1784.620	1784.795	136.60	13.38
7	16628-1.2	1784.907	1784.795	1784.982	82.63	8.56
8	16628-1.3	1785.107	1785.032	1785.219	57.81	5.21
9	16628-1.4	1785.305	1785.232	1785.369	32.31	2.65
10	16628-1.5	1785.505	1785.456	1785.569	17.67	1.12
11	16628.10019.4	1905.974	1905.874	1907.031	12.63	1.00
12	16628.10019.3	1907.173	1907.045	1907.273	22.54	2.11
13	16628.10019.2	1907.373	1907.287	1907.444	33.86	2.91
14	16628.10019.1	1907.572	1907.458	1907.701	34.87	3.30
15	16628.10019.0	1907.772	1907.701	1907.843	20.93	1.55
16	16628.10019.1	1907.972	1907.900	1908.043	21.03	1.55
17	16628.10019.2	1908.157	1908.085	1908.271	10.97	0.90
18	16628.4	2229.874	2229.679	2230.029	27.51	4.87
19	16628.3	2230.146	2230.029	2230.263	111.72	16.23
20	16628.2	2230.380	2230.263	2230.516	225.18	32.39
21	16628.1	2230.633	2230.516	2230.770	280.66	40.90
22	16628.0	2230.887	2230.770	2231.023	287.24	41.95
23	16628.1	2231.140	2231.023	2231.257	242.23	34.17

Figure 76

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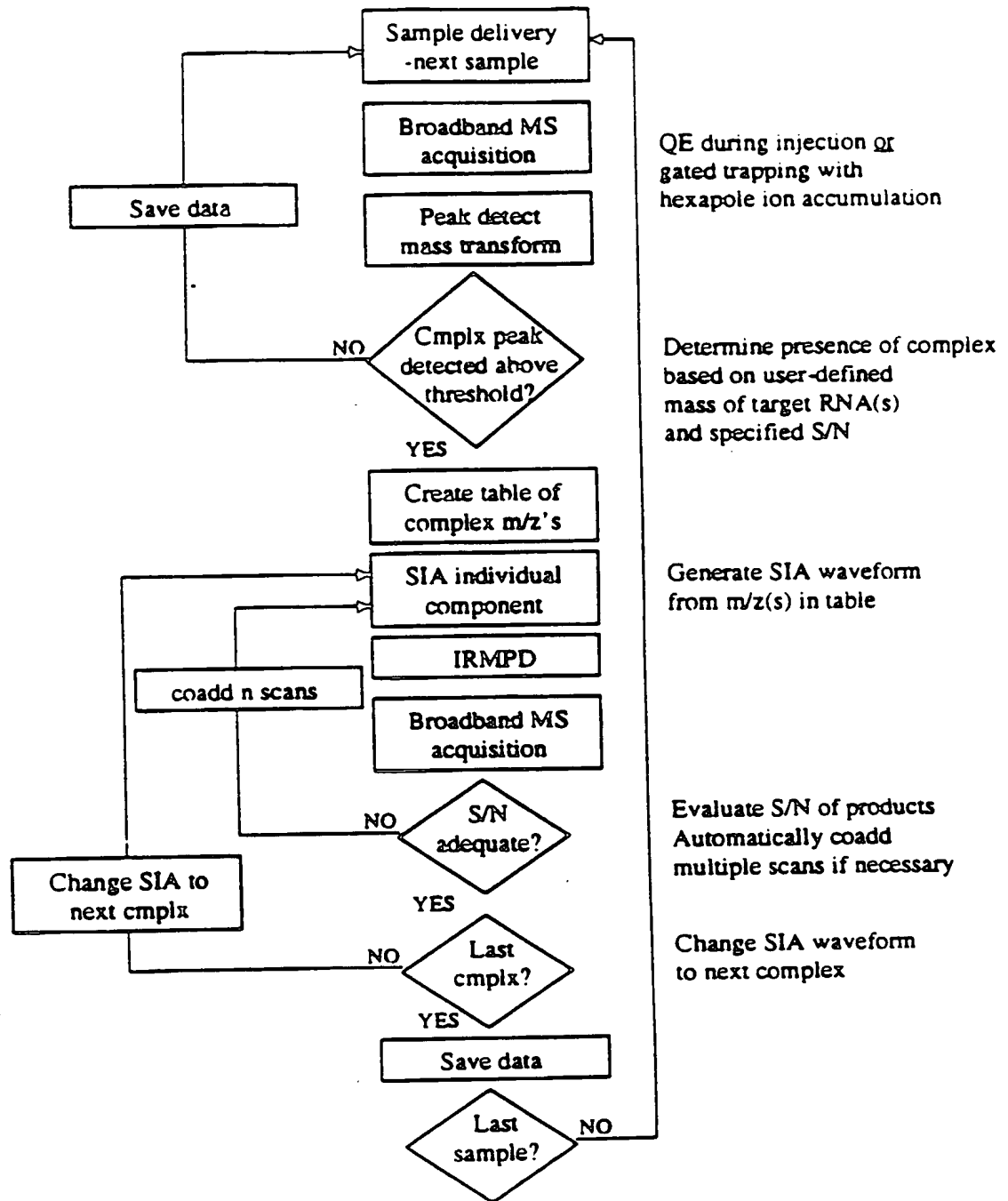


Figure 77